Reply

We would like to address some of our specific replies upfront:

1) The USPTO 06-09-2010 Office Action (OA) (at page 28 line 11-19) said that with off-label use of claimed therapeutic method – if "results obtained were clearly superior to those seen in the prior art for the current standard of care, (e.g. antidepressant monotherapy) then an affidavit or declaration under 37 CFR 1.132 summarizing the results obtained in the Applicant's own practice and comparing them to what has been observed in the prior art, for example in clinical trials of antidepressant monotherapy, could suffice to establish unexpected results and the satisfaction of a long felt need. Such results could take the form of an observation of reduced suicidality... for example."

So that would establish one way to get the patent issued. We are considering such an avenue, but based on the examiners' statement in the last OA (page 28 last two lines -page 29), we feel that the patent can be issued even without going to into this route.

> A call to the USPTO Inventor Assistance Center (IAC) [ref# 1178736632] on 11-19-10 also revealed that as long as this applicant can show an evidence that I hired research organizations doing the needed research, that would satisfy for being my product and then I can provide the requested declaration. Said research can take place in the future and does not have to be done prior to our priority date.
> Furthermore as long as applicant feels a chance for getting the patent issued, the applicant can file for RCE.
>
> The IAC also disclosed that the secondary considerations are not limited only if that is based on research. While the IAC concurred with what the examiners said that is that the secondary considerations cannot be based on arguments, but the IAC added that that is because arguments are opinion. So the IAC clarified, that if the arguments are based on facts than the secondary considerations can be relied on for patentability.

2) Furthermore the examiners on page 28 (last two lines) and page 29 also reveal other ways on how the "prima facie" obviousness can be overcome:

> "Furthermore, a prima facie case of obviousness can be overcome if the prior art **teaches away** from modifying the prior art in the claimed manner. *In the instant case, the prior art teaches an antidepressant effect for antipsychotic medications or combinations of these medications with antidepressants.* However as mentioned previously the prior art does not specifically recommend using these agents as an initial therapy Therefore if it were established that the prior art specifically criticized or discouraged using antipsychotics as initial therapy, this could overcome the finding of obviousness It is suggested that if Applicant is aware of publications representative of the state of the prior art, for example clinical guidelines or review articles, that specifically disparage or criticize the use of antipsychotics as initial therapy for non-psychotic depression, that **submitting these publications in an information disclosure statement could overcome the finding of obviousness** if the references are sufficient to establish a widespread consensus in the art at the time of filing against using the claimed invention as initial therapy."

It is respectfully submitted, that we have listed the requested references that are teaching away. We have listed <u>some</u> of those in our utility and again in our reply to the last office action(OA) (page 11-12).

For your convenience we paste these here again:

> From page 1 lines 30-to page 2 lines 1-14 of our utility:
> While chlorpromazine was used early on in the treatment of depression, as tricyclic antidepressants became available the use of antipsychotic medications declined, and they were never widely used in the treatment of depression in the absence of psychotic symptoms. See also Raskin A. et al 1970, p.170: "There is a persistent belief that these drugs (antipsychotics) are not very effective in the treatment of depression". In general, the use of antipsychotic drugs was reserved for use in patients having psychotic symptoms. It was generally accepted that antipsychotic drugs used alone could not treat major depressive disorder. In fact, it was thought that antipsychotic drugs, including some of the atypical antipsychotics, may even have depressogenic properties. (Harrow, M. et al 1994, Galdi J. 1983, Tollefson, G.D. et al 1998, Maguire, G.A. 2002, Cookson I.B. et al.)
> In contrast to antidepressants, antipsychotics alone (including the atypical antipsychotic risperidone) were ineffective in the chronic mild stress (CMS) model (animal simulation of depression) (Papp, M. et al 1996; Papp, M. et al 2000). In sum, many studies showed that antipsychotics do not have significant antidepressant activity and, if anything, may cause a depressogenic effect.
>
> From page 4 from lines 22 and the last paragraph of our utility:
> "Thus, to date, the use of atypical antipsychotic medications has been restricted to their use in combination with antidepressants, for the treatment of the following subtypes of illness: schizoaffective disorder; psychotic depression; bipolar (manic-depressive) disorder; and treatment-resistant depression. In all of these categories, the use of antipsychotic medication may be expected due to its effects on contributory psychosis, or severe agitation.
> There have been no reports recommending that the combination therapy can or should be used for a major depressive disorder, or for other depressions as an initial treatment, upon initial presentation to a health care provider (or as soon as possible), or for using the combination as a treatment of first choice, for reducing the risk of suicide."

In addition, it is notable that the PTO's above quoted statement as regards to:

"In the instant case, the prior art teaches an antidepressant effect for antipsychotic medications or combinations of these medications with antidepressants." – is incorrect as the cited prior art references by the PTO do not teach initial treatment with the method (they only make an overgeneralization in their claims – without guidance, experiments or sufficient enablement – of the method to be used for depression or going to the extreme in some cases for example suggesting to be used "for all neuropsychiatric disorders"). No experiments or guidance is provided in any of these cited prior art references as how and why the method could be used (e.g. as initial treatment; or to overcome the paradoxical effects of antidepressants causing suicide; to be used for "relapse prevention"/inhibiting relapse; or for treating residual symptoms of depression). The secondary factors also supports that the authors and the major drug companies behind these prior art documents were not aware of our invention and were not using or not pursuing further their patent applications that in many cases went abandoned. However, there is more:

In the enclosure of our reply to the first OA we have included references that were teaching away even after our priority date and even after the publication of our patent application:

(From the PTO's last **OA** page 29):
"Therefore if it were established that he prior art specifically criticized or discouraged using antipsychotics as initial therapy, this could overcome the finding of obviousness It is suggested that if Applicant is aware of publications representative of the state of the prior art, for example clinical guidelines or review articles, that specifically disparage or criticize the use of antipsychotics as initial therapy for non-psychotic depression, that submitting these publications in an information disclosure statement could overcome the finding of obviousness if the references are sufficient to establish a widespread consensus in the art at the time of filing against using the claimed invention as initial therapy."

The widely taught and accepted "Texas Algorithm" July 2004 Arch Gen Psych p671 teaches the following [in 2004 – two years after our priority date].
Please note that about half of the US states have implemented the Texas Algorithm project at least starting this with the module to treat schizophrenia with plans to implement it for bipolar disorder and major depressive disorder as well. These are different Algorithms; here we only list the one aimed treating non-psychotic depression (see next page).

[Following that (on page 6, 7, and 8) there are other well-recognized teaching away references].

See next page for the teaching away of the Texas Algorithm:

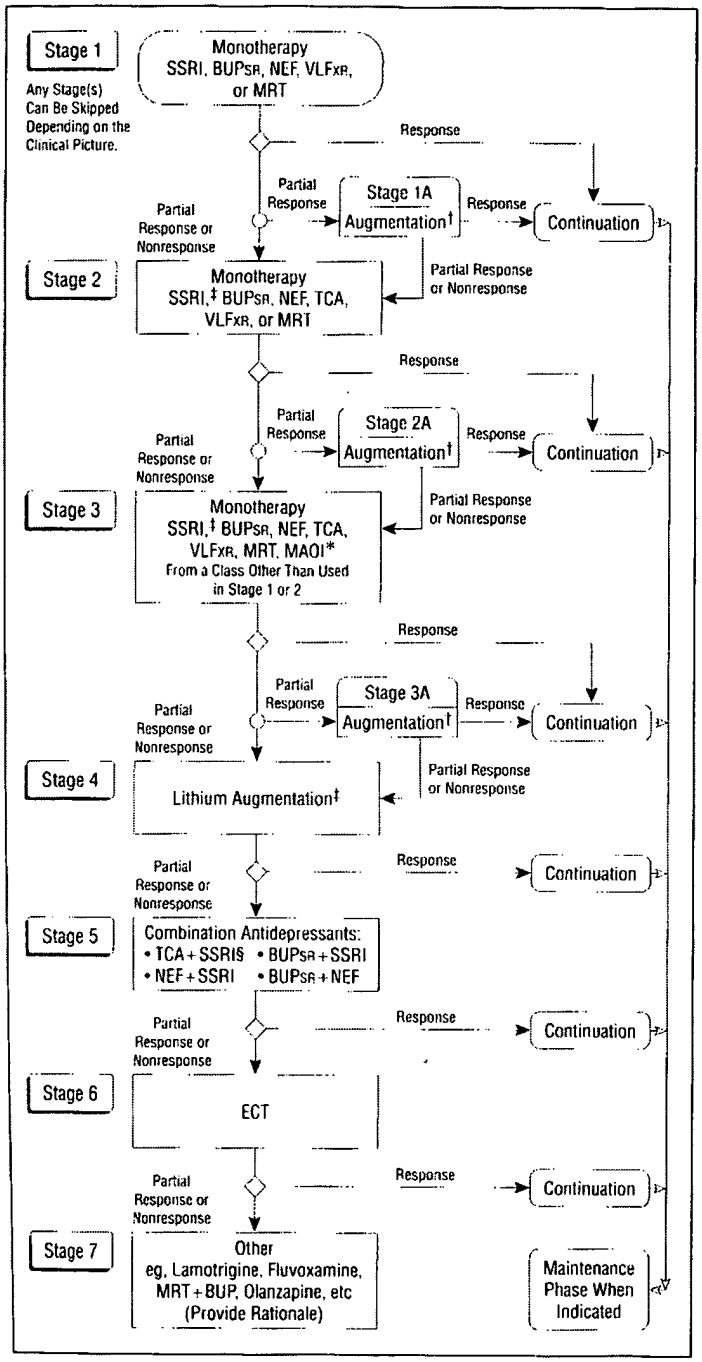

Figure 1. Strategies for the treatment of nonpsychotic major depressive disorder. Asterisk indicates consider TCA/VLF if not tried; dagger, lithium, thyroid, buspirone; double dagger, skip if lithium augmentation has already failed; section mark, most studied combination. BUP_{SR} indicates bupropion sustained release; cital, citalopram; fluox, fluoxetine; MAOI, monoamine oxidase inhibitor; MRT, mirtazapine; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants; VLF_{XR}, venlafaxine extended release. This figure is published with permission from the Texas Department of Mental Health and Mental Retardation and is part of a state-funded project.

Texas Algorithm July 2004 Arch Gen Psych p671

Berlin Algorithm Project -in Aldi 2003 was teaching against as well:

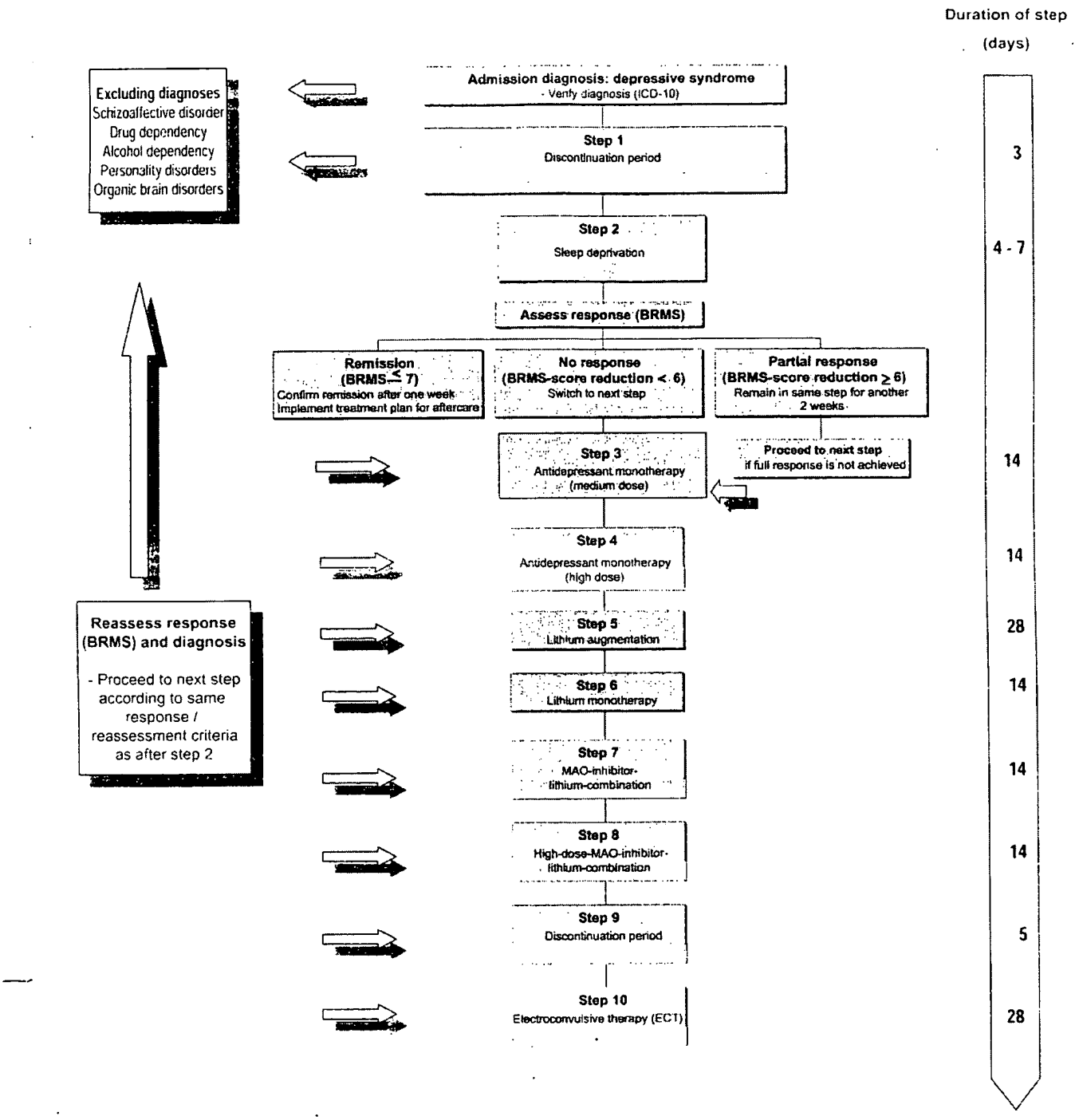

Fig. 1 The Berlin Algorithm Project, Phase 2: randomised controlled clinical trial comparing a standardized sequential drug treatment regimen (SSTR) with treatment as usual (TAU) and algorithm-guided decision making (BRMS = Bech-Rafaelsen-Melancholia-Scale; MAO = monoamine-oxidase)

Berlin Algorithm Project -in Aldi 2003

Aldi, M. et al Algorithms for optimizing the treatment of depression: Making the right decisions at the right time. Pharmacopsychiatry 2003; 36 Suppl 3: S222-S229.

Algorithm Study of the German Research Network on Depression -in Aldi 2003 again was teaching away:

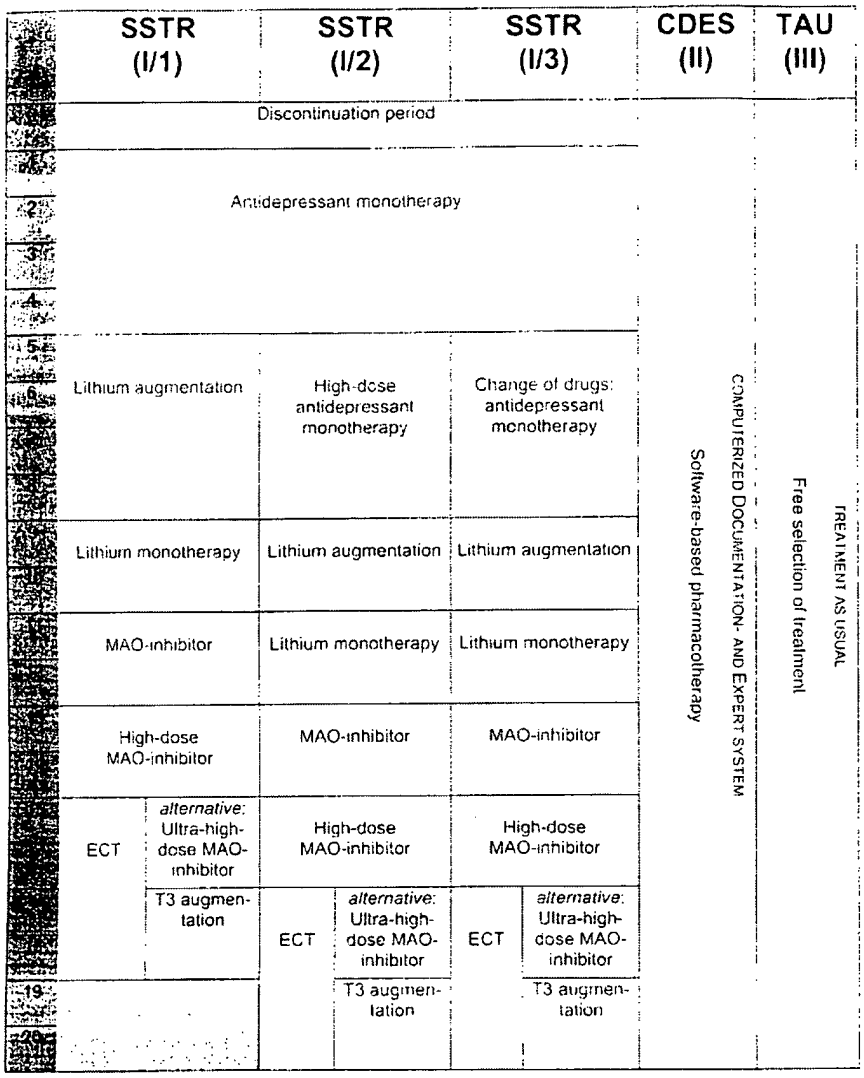

Fig. 2 The Algorithm Study of the German Research Network on Depression (SSTR = standardized stepwise drug treatment regimen, CDES = computerized documentation and expert system, TAU = treatment as usual, MAO = monoamine-oxidase inhibitor, ECT = electroconvulsive treatment, T3 = trijodthyronine)

Algorithm Study of the German Research Network on Depression -in Aldi 2003Aldi, M. et al Algorithms for optimizing the treatment of depression: Making the right decisions at the right time. Pharmacopsychiatry 2003; 36 Suppl 3: S222-S229.

STAR*D -NIMH funded study -in Aldi 2003 was again teaching away:

Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (www.star-d.org), a NIMH-funded, multisite clinical trial is currently underway in the United States. STAR*D prospectively evaluates stepwise treatment procedures in depression

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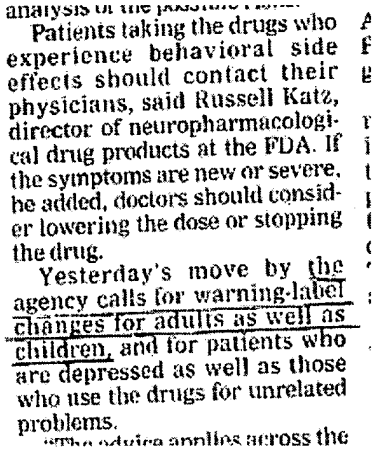
STAR*D –(**stepwise** treatment procedures in depression) - NIMH funded -in Aldi 2003
Aldi, M. et al Algorithms for optimizing the treatment of depression: Making the right decisions at the right time. Pharmacopsychiatry 2003; 36 Suppl 3: S222-S229.

The PTO is also raising the issue that the teaching away references should be representative of the prior art. As said before, **there is not one but multiple references and the teaching away continued even after the publication of our patent application**. The Texas Algorithm was widely accepted by about half of the US states (meaning that they even took action and implemented the Texas Algorithm, and in many states they were even making it mandatory in state facilities in the context stated above). [As a first hand knowledge with absolute certainty the state made it mandatory in state facilities in the State of Pennsylvania with plans of making it mandatory for other diagnostic categories as well]. So one can conclude that the Texas Algorithm in general and as related to the treatment of non-psychotic depression must have been pretty much "representative". The other Algorithms (pasted above) were also funded by governmental agencies, as I understand that. STAR*D – **stepwise** treatment procedures in depression - was an NIMH funded huge project, and I would say that that the **National Institute of Mental Health is a pretty much recognized agency**, so the study they fund (especially in case of a such an expensive multicenter study) **has to be representative**.

Please also note that the Texas Algorithm, and the Berlin Algorithm Project are also addressing partial response. Therefore secondary factors for our claims on treating residual symptoms of depression would also be supported by these teaching away publications even though – as we have addressed this in our earlier replies there is a difference between partial response and residual symptoms. (e.g. see our reply to the 4th OA [March 11, 2009] page 168 starting with paragraph "Documents from Tollefson...). None of the above references teaches the treatment with our method for the residual symptoms in non-treatment resistant depression (non-TRD).

So it seems that we have satisfied the requirement asked by the examiners, and we have supplied the required publications to overcome the finding of obviousness. As a result, it is respectfully submitted that our Claims are in proper form for issuance of a Notice of Allowance and such action is respectfully requested at an early date.

Furthermore:
In addition, when the FDA director was interviewed on the new FDA warning on the antidepressants causing suicide, he was teaching away from our invention, suggesting decreasing or stopping the antidepressant (leaving patients having suicidal thought and their doctors with very limited options). This has happened after our patent application. So secondary factors intensely support that prior art did not anticipate our invention, and they were teaching away from it:



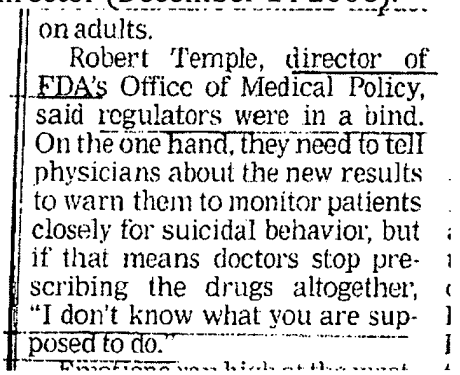
analysis of the possible risks.

Patients taking the drugs who experience behavioral side effects should contact their physicians, said Russell Katz, director of neuropharmacological drug products at the FDA. If the symptoms are new or severe, he added, doctors should consider lowering the dose or stopping the drug.

Yesterday's move by the agency calls for warning-label changes for adults as well as children, and for patients who are depressed as well as those who use the drugs for unrelated problems.

The advice applies across the

In addition most recreantly this teaching away repeated itself as demonstrated by another front page interview with a different FDA director (December 14 2006).



on adults.

Robert Temple, director of FDA's Office of Medical Policy, said regulators were in a bind. On the one hand, they need to tell physicians about the new results to warn them to monitor patients closely for suicidal behavior, but if that means doctors stop prescribing the drugs altogether, "I don't know what you are supposed to do."

Physicians were high at the event

The FDA is perplexed about the lack of solution (and seemingly unaware of our solution or application and PTO publication). (The FDA never contacted us asking for any further information). The FDA director stated that he does not know what he is supposed to do [or suggest].
(Please see the FDA director's statement below with the full article also enclosed.)

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Antidepressants may have suicide risks

FDA urges drugmakers to place warnings on medications.

BY THE WASHINGTON POST

WASHINGTON — The federal Food and Drug Administration urged drug makers Monday to put new warning labels on popular antidepressant medications, including Paxil, Zoloft and Luvox, alerting doctors and consumers to watch for suicidal tendencies, hostility and agitation in patients taking the drugs.

The agency's action focuses on 10 anti-depressant drugs in all and follows a warning by the British government last year advising physicians not to prescribe most widely used antidepressants to children. Last month, families of American adolescents who killed themselves while taking the medications implored the FDA to take comparable steps, and an expert advisory committee urged greater vigilance in the use of the medications in children with depression.

The agency said it does not know whether the medications — which include several drugs known as selective serotonin reuptake inhibitors, or SSRIs — are responsible for reported side effects such as inner restlessness, agitation and suicidal thoughts in some people. Officials said they are drawing greater attention to known cautionary information while a team of outside researchers completes a comprehensive analysis of the possible risks.

Patients taking the drugs who experience behavioral side effects should contact their physicians, said Russell Katz, director of neuropharmacological drug products at the FDA. If the symptoms are new or severe, he added, doctors should consider lowering the dose or stopping the drug.

Yesterday's move by the agency calls for warning-label changes for adults as well as children, and for patients who are depressed as well as those who use the drugs for unrelated problems.

"The advice applies across the board whether the drugs are used for any indication — psychiatric or not," Katz said.

Critics of the medications called yesterday's move a victory and demanded that the FDA go further. Although Prozac is the only one of this class of drugs that has been specifically approved to treat depression in children, doctors are writing tens of thousands of prescriptions for many of the others, based on their clinical judgment that the drugs are safe and effective.

"Doctors are going to be on the line not to prescribe them as if they were pacifiers," said Vera Hassner Sharav, president of the Alliance for Human Research Protection, a patient advocacy group based in New York.

Many critics complain that a majority of studies of the drugs in children found the medications did no better than dummy pills in treating depression, but that these studies have been hidden from doctors and the public. The companies say the studies are proprietary.

Sharav and other critics charge that the FDA and the American psychiatric establishment, which has broadly supported the efficacy of the drugs, have been unduly influenced by the pharmaceutical industry. Dozens of lawsuits against the medications have been filed.

Many psychiatrists say the medications save lives and warn that discouraging patients from taking them could lead to greater numbers of suicides. They say suicidal tendencies or attempts among patients taking the drugs are the result of underlying disorders, not the medications.

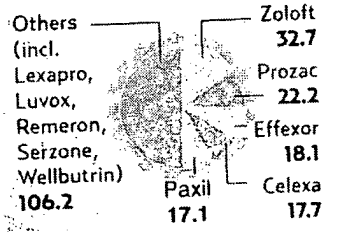
The drugs affected by yesterday's announcement are Prozac, Zoloft, Paxil, Luvox, Celexa, Lexapro, Wellbutrin, Effexor, Serzone and Remeron.

Antidepressants, use with caution

The Food and Drug Administration recommends that certain antidepressants include a warning for worsening depression or suicidal thoughts. There were over 213 million dispensed prescriptions for antidepressants in 2003.

Dispensed prescriptions for antidepressants, 2003

in millions



SOURCE: IMS Health AP

Pittsburgh Post-Gazette

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FDA may expand alert on drugs for depression

By Shankar Vedantam
The Washington Post

WASHINGTON -- Widely used antidepressants double the risk of suicidal behavior in young adults, from around 3 cases per 1,000 to 7 cases per 1,000, according to a huge federal analysis of hundreds of clinical trials. It marks the first time that regulators have acknowledged that the drugs can trigger suicidal behavior among patients older than 18.

Food and Drug Administration officials yesterday said the higher risk was found in patients between 18 and 25, and that the risk faded among older patients. The finding comes two years after the agency ordered a "black box" warning on the drug labels following discovery of a heightened risk of suicidal behavior among children taking the pills.

After reviewing the latest data, an expert federal panel yesterday recommended that agency officials tell doctors and the public of the risk, but also find a way to note that the risk declines with age — and that leaving depression untreated is also risky.

While the studies on the relationship between the drugs and suicide appear contradictory, the experts said one possibility is that the drugs may pose a risk early in treatment, but have a protective effect in the long term.

The agency is leaning toward expanding its black box warning, said Thomas Laughren, director of FDA's division of psychiatric drug products. Officials said they will try to craft language that would urge clinicians to use the drugs carefully, not abandon them.

The new finding created a dilemma for the regulators. Even as it vindicated some of what critics of drugs such as Prozac, Paxil and Zoloft have said for years, the earlier official

SEE **FDA,** PAGE A-6

FDA may expand alert on drugs for depression

FDA, FROM PAGE A-1

warnings about the drugs appear to have led to a drop in their use -- and there are troubling signs that this, too, can lead to an increase in suicides.

After concerns were raised in the Netherlands about the suicide risk, there was a 22 percent drop from 2003 to 2005 in antidepressant prescriptions for patients below 18, and a 50 percent increase in suicides, University of Illinois psychiatry professor Robert Gibbons said. The number of suicides went from 34 to 51.

"What we are seeing is the early signs of an epidemic of suicide in children who are no longer being treated for their depression," Mr. Gibbons said in an interview. U.S. suicide data for 2005 is not yet available, but Mr. Gibbons said the FDA's black box warning had caused a similar decline in prescriptions among children in this country. He predicted dozens of additional suicides as a result, and warned that any expansion of the black box would have a similar impact on adults.

Robert Temple, director of FDA's Office of Medical Policy, said regulators were in a bind. On the one hand, they need to tell physicians about the new results to warn them to monitor patients closely for suicidal behavior, but if that means doctors stop prescribing the drugs altogether, "I don't know what you are supposed to do."

Emotions ran high at the meeting yesterday of expert advisers, with both advocates for the drugs and their critics warning the federal regulators that a wrong move would cost lives.

Critics of the drugs said they were deeply distrustful of both the medical profession and the FDA itself because of conflicts of interest with the pharmaceutical industry. Allen Jones, of the consumer advocacy group Alliance for Human Research Protection, said, "The love affair between the pharmaceutical industry and our government institutions has to end."

Gwen Olsen, a former pharmaceutical industry representative, told the panel that she had influenced doctors by offering them free food, gifts and gimmicks to gain access to them, and then presented them with skillfully manipulated data.

Ms. Olsen said she had a change of heart after her 20-year-old niece committed suicide following a withdrawal reaction from the antidepressant Paxil. She said her niece first tried to hang herself from a ceiling fan. When the fan broke, Ms. Olsen said, she doused herself in oil and set herself alight.

Two experts critical of the drugs, British psychiatrist David Healy and Joseph Glenmullen, a psychiatrist who lectures at Harvard, said the FDA analysis played down the magnitude of the suicide risk. Information uncovered in lawsuits, they said, suggested that several suicides in industry trials were never disclosed.

"Industry controls the data, and industry, with the aid of FDA, have miscoded the data, so all the articles in all the journals that purport to represent clinical trial data are misleading," Dr. Healy said in an interview. His own analysis, published in the British Medical Journal in 2005, found a twofold increase in risk among all adults taking the drugs. "The idea you would have a risk in one age group but not another is just wrong," he said.

Other medical experts and patient advocates warned, however, that black box warnings could scare away patients from necessary treatment.

So it seems that we have satisfied the requirement asked by the examiners, and we have supplied the required publications to overcome the finding of obviousness. As a result, it is respectfully submitted that our Claims – as amended - are in proper form for issuance of a Notice of Allowance and such action is respectfully requested at an early date.

In addition, - as regards of claim rejections 35 USD § 112 (page 5 of last OA), the examiners stated:

"Claims 140, 141 , 143, and 144 are rejected under 35 u.s.c. 112, first paragraph, as failing to comply with the written description requirement The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention Applicant's amendment submitted March 13, 2009 with respect to the aforementioned claims has been fully considered and but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for a method comprising discussing all of the specific considerations recited in the claims with a patient. Although the specification and the priority document 60/319436 **do disclose these factors as considerations for physicians to take into account in the treatment of depression, they do not teach or disclose discussing them with a patient**. As the instant specification as filed contains no description of this method the specification as originally filed does not provide support for the subject matter of instant claims 140, 141 , and 143. See in re Smith, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972)"

It is respectfully submitted, that:

In page 110 of reply to the 2nd OA [August 25, 2007] we had

Amendments to the specification (pasted from the provisional application):

PTO page 31of 88: 0226 line 5 on – till page 32 0229 line 2; (=my copy with font 14 [also enclosed] it is page 43 2nd paragraph line 5-23.):

"As in all treatment,...
we are **involving them [our patients] in the decision-making**, but we are supposed to discuss with them the *risks/benefits,* side effects of the medications, and *available alternatives* anyway."

Therefore, **all reasoning that are used to convince the physicians to use our method can and should be discussed with the patients within the framework of discussion of *risks/benefits,* side effects of the medications, and *available alternatives*.** We have said that we should be involving the patient in the decision-making!

The PTO examiners have also acknowledged that the discussion of *risks/benefits,* side effects of the medications, and *available alternatives* are part of the standard treatment.

Claim 140 specifically includes: "physician or other health care provider is involving said patient in the decision-making of said method by discussing with said patient the *risks/benefits,* side effects of the medications". In claim 141 "other added benefits" and in claim 143 "reasons and other rationales" are within the essence of these claims. **How can the doctor discuss the risk/benefit and available alternatives with the patient if not discussing the rationale for the use of the method with the patient? That is not possible.**

Therefore Claims 140, 141 , 143, and 144 **cannot** be rejected under 35 u.s.c. 112, first paragraph, as failing to comply with the written description requirement, as all of the specific considerations recited in the claims were included in the specification.

So it seems that we have satisfied the requirement asked by the examiners, and we have supplied the required publications to overcome the finding of obviousness. As a result, it is respectfully submitted that our Claims – as amended - **are in proper form for issuance** of a Notice of Allowance and such action is respectfully requested at an early date.

Sometimes (in a reply) saying less is more, however for completeness sake we have to present more information.

The above have satisfied the requested requirements for the issuance of the patent for the known antidepressants.

The examiners in the last OA page 22 lines 8-9 already acknowledged "It is never alleged that previously known antidepressants, for example citalopram, paroxetine, fluoxetine, and so forth, are non-enabled."
However, the applicant feels that **enablement had been provided even for the group of [class of] medications (antidepressants)**. So we do not want to confuse the examiners with the following, but rather reiterate of what was said before in the previous replies. So we summarized below our (more then) plausible **theoretical basis** of how and why the combination treatment would work for the various claims that includes initial treatment, relapse prevention/inhibiting relapse, and treating residual symptoms of depression. Please note that these discoveries were missed by prior art, and we had to rely on multiple discoveries in a row in order to draw the needed conclusions to come up and support our invention.

> While this enablement all relies on our provisional application including the need of a new and more sensitive test for depression; in Application Serial Number 11/034,447 we further elaborated with some added (optional) examples and a sample test.

At page 23 of the last OA (lines 4-6) the examiners mention that lack of enablement could be overcome by two ways A) by providing a plausible theoretical basis – that we reiterate herein – or B) by a convincing experimental data.

The following boxed (stepwise) explanation [A) to E) – where each explanation is relying on the previous one] we are providing the enabling theoretical basis of our invention – that would satisfy also for the broader group (class) of medications. So hopefully that would be acceptable to the examiners. Please note that the guidance we provided for our invention is not limited to the following (paraphrased) summary.

The following is also worth revisiting: The PTO examiners basically throughout all of the OAs have been puzzled that "how come going against the teachings of prior art and against the standard of care existing at the time (before our invention) and without others providing a rational for the use of the method, (that goes against the teaching away) could have been a malpractice ("for others"); and how come it would not be a malpractice for this applicant who was providing a new rational (missed by others) and who established with new guidance and enablement for a new standard of care. This applicant came up with new information for changing the balance for the decision-making that would allow the use of the instant claims that was not possible before. That is the PTO examiners were perplexing of how can a new invention (with new guidance) make a 180 degree turn in the clinical practice. The health care providers that I shared my reasoning had no problem at all of following and accepting that concept, or the innovative logic behind what is disclosed in the box below. It is also notable that when I asked health care providers for participate in a "mock trial" that I will present below in the boxed area, I had a different motivation and did not envision at that time to share that with the PTO. However because it is so convincing (and relevant) I share that herein:

(Stepwise) explanation on the **enabling** theoretical basis of our invention – that would satisfy **also for the broader group (class) of medications**:

The examiners in the last OA page 22 lines 8-9 already acknowledged "It is never alleged that previously known antidepressants, for example citalopram, paroxetine, fluoxetine, and so forth, are non-enabled."

Summary:

1) Mock trial. This shows that the existing algorithms for the treatment of depression is obsolete, and the new standard of care of initial combination treatment of our method should be in place to save the most lives. Violation of that new standard of care would be a malpractice (unless the patient is refusing it after all the key facts discussed herein are presented to them).

A) This section is a critique of the current screening and testing of depression because it is missing critical symptoms. Solution with our extended symptom list (not included in the DSM diagnostic criterion set) can recognize patients suffering from depression that are missed with the current screening methods. Elaborate on the problem with DSM and "SIGECAPS" acronym. Help PCP's (primary care doctors) and psychiatrists to recognize depression effectively by relying on the new test, so that more patients would get help.

B) Certain (extended) depressive symptoms – as we drew attention to that - are specifically targeted by medications (like with the combination treatment) that would have additional and a cascade effect. Reveal new information on placebo and the targeted conditioning ["pseudo-placebo"] effects that were not recognized previously but should have an important role in our understanding of treatment and in improving efficacy.

C) Further educate patients on relapse prevention, full recovery and lasting remission, and how and why the combination treatment would be useful for this purpose. (Share of what we already know about relapse prevention – and how that relates to combination treatment). Also tell how the combination treatment and atypical antipsychotics/dopamine system stabilizer target many of the unrecognized – extended depression symptoms – from our new test that we discussed above under A).

D) Show how our discovery and education on the neuroplasticity of depression explains how the combination treatment would be working (in light of A, B, C, explained above). This also helps removing the bias, the stigma against mental illness, so that more patients would accept treatment.

E) (This #E is a partial support for further enabling our method and is a strategy with different focus then #1 [mock trial] above).
Let's give patients an immediate reinforcement and a new personal experience that change is possible. Start combination treatment right away and give the treatment the patients need. Balance the initial assessment (the initial intake interview) with intervention. In the past the assessment was almost a dwelling in the patient's problem – combine assessment with treatment/therapy and education, and change the patients basic believes.
That means more patients would accept treatment and less would discontinue their prescriptions.

1) In this section we will present a "mock trial". Let's leave no room for the doctors but to follow our lead and be absolutely convincing that the initial treatment with the combination treatment should be the new standard of care and should be discussed with the patients.

How can we change the current psychiatric practice about the treatment of depression? How can we change the opinion of the doctors and health care providers within a few minutes?

I have pre-tested my approach and invited some nurses and mental health workers to be my "jury" in a mock "trial".
I was surprised of how strong they agreed with me, some even offered to share their opinion on camera for free. I got a 100% "verdict" that those who are not willing to change and not willing to discuss and offer the combination of antidepressant-atypical antipsychotics/dopamine system stabilizers as an initial treatment for depression would be liable for malpractice.

So here is how I presented the facts for the "mock trial":

"I'd like to convince others that the treatment of depression should be vigorously treated early on as an initial treatment with the combination treatment to prevent suicide.

I'd like to get your opinion, that if we have a risk management principle that we apply in all other areas of medicine why would we not use that same principle in psychiatry to save lives?

The clinicians have a responsibility of not only weighting the risk of the individual but also the risk of a group. This is because we do not know who in the group would be affected.

This had been customary for long, in the medical practice.
I clearly remember that as a medical student we were taught that principle and the standards in the treatment of appendicitis. If the patient showed some typical symptoms that he or she *might* have appendicitis (specifically if the WBC and sedimentation rate were also elevated suggesting inflamation), then the surgeon was operating on. The surgeon had rather operated on healthy people for whom it turned out on the operating table that they did not had an infected appendix, (taking out the appendix anyway), then wait until it became obvious that the appendix had perforated. This is quite a standard medical principle, a procedure that surgeons followed. The risk of dying from the operation (without an infected appendix) was far less compared to waiting and having the (high) risk of death from operating late with a perforated appendix. (This principle has not changed but now we are also doing a CT scan where it is available right away).

We are following similar procedures and we give thiamin routinely for everybody in the emergency room before giving IV glucose, (therefore preventing Korsakov's syndrome in alcoholics). We are routinely testing for drug screen in the ER (and the patient gets charged for the cost); even when the patient says that he or she is absolutely not taking any illicit drugs.

[[In Japan where the incidence of gastric cancer is approximately 4 times that is found in the United States, the public has accepted a mass-screening program with all the risk of gastroscopy, cytology and biopsy.]] [This section in [[ ]] was added as an optional additional example, and that was not in the provisional application].

This is a standard procedure and good clinical practice. The risk of being operated on or getting a blood or

urine drug screen is not the same. Nevertheless, we take into account the risk/benefit for a group not just for an individual. So why are we not more vigorous in preventing suicide?"

I asked if they are following me and if they are in agreement with me so far; and the "mock jury" concurred. In fact they were ready to give the "verdict".

I also shared that since I started to advocate for the use of the combination treatment about 10 years ago, there have been two publications a case report and a placebo controlled trial showing in the direction stated in my claims that antipsychotics can and should be used for the prevention of suicide. (These publications showed that reducing suicidality in depression is superior with the combination therapy of an atypical antipsychotic and an antidepressant compared to antidepressant monotherapy).

(Viner MW et al Low-dose risperidone augmentation of antidepressants in nonpsychotic depressive disorders with suicidal ideation. Journal of Clinical Psychopharmacology 23:1 2003.
Reeves H et al Efficacy of risperidone augmentation to antidepressants in the management of suicidality in major depressive disorder: a randomized, double-blind, placebo-controlled study. J. Clin Psychiatry 69:8 August 2008)

In fact the placebo controlled trial from 2008 (Reeves) showed a total of 42% decrease of suicidal scores in the combination treatment that was about double then those that continued on antidepressant only (and placebo).

I asked the jury again in this "mock trial" if I would get their verdict. I asked if in a theoretical case I would have been the expert witness testifying, would they agree that it would be a malpractice of not discussing and not offering to the patient with non-psychotic unipolar depression the combination treatment to be started right away as initial treatment? I reminded the jury that the same standard of care the same risk management principles are used in all other areas of medicine, namely that the clinicians have the responsibility of not only weighting the risk of the individual but also the risk of a group. This is because we do not know who in the group would be affected.

The "mock jury" concurred.

The statistics also speak for themselves:
28-44% of depressed patients exhibit violent behavior (Hughes, D.H. 1998) and 30-40% displays anger attacks. (Koh, K.B. et al. 2002).
Approximately 25% of patients at suicide risk do not admit to being suicidal. (However, in most cases they had communicated suicidal ideation or intent to family members.) (Fawcett cit#18. < also referenced in: Simon, R.I., 2002).
1 in 6 patients with MDD seen by a psychiatrist commits suicide.
About 15% to 20% of all patients with serious affective disorder will kill themselves. (Forster P., 1994.).
The odds are much higher for an adverse event or for a lethal outcome then in the case of appendicitis.
We need to treat depression more vigorously with the initial combination treatment.

The algorithms that continued teaching against our published invention and that keep suggesting starting the treatment of depression with single antidepressants are obsolete and harmful even if they are from recognized authors, institutions, or governmental research entities. (Texas Algorithm July 2004 Arch Gen Psych p. 671, Berlin Algorithm Project – Algorithm Study of the German Research Network on Depression, – STAR*D

Sequenced Treatment Alternatives to Relieve Depression – NIMH funded [all in Aldi M. et al 2003 Algorithms for optimizing the treatment of depression: Making the right decisions at the right time. Pharmacopsychiatry 2003; 36 Suppl 3: S222-S229.]

We cannot hide under the excuses of potential side effects or rare side effects like Neuroleptic Malignant Syndrome and Tardive dyskinesia, when new atypical antipsychotic and dopamine system stabilizer is available with lowered risk. In addition the risk benefit analysis with the statistics shared clearly would shift the decision to the initial treatment to save the most lives.

However, to show how easy it would be to get the sympathy of the "jury" and even to make a case of negligence, (for those who would hang on to the old dogmas) I continued:

Another strong argument for our initial treatment of the combination treatment comes from looking at the statistics. It had been noted in the literature that the focus should be on the characteristics of those who commit suicide rather than on the characteristics of patients with suicidal ideation. About 15-20% of all patients with serious affective disorder will kill themselves. On the other hand 8% of Borderline Personality Disorder (BPD) patients will commit suicide. With the BPD patients, who "bother" the psychiatrists or even wake them up at the middle of the night while getting admitted to the hospital we psychiatrists are not hesitant to use polypharmacy, to give antidepressant-antipsychotic combination, or even to give clozapine with its high risk. This is in contrast to patients with Major Depressive Disorder (MDD) who suffer and die silently, even if they have a 2 – 2 and ½ times more risk for completed suicide – as they do have – and where we strangely have established a different standard withholding the combination treatment. This approach by us psychiatrists can no longer be maintained.

In the argument to consider, or start using the combination treatment right away in all those who are clinically depressed, it is the decrease of suicide rate that is the paramount important factor.

I not only won the "verdict" I was looking for, but I have seen the emotional involvement of the "jury" as they concurred with me 100%.

The above is strong enough evidence that did convince the "jury" in our mock trial that the medical standard is to take into consideration the interest of the group as we do not know who in the group would be affected. So the standard of care should be the initial treatment with the combination treatment to save lives.
The risk benefit and available alternatives and no alternatives have to be discussed with the patients and this must be documented in the chart. It had been discussed in risk management classes that lack of this discussion and the lack of that documentation is considered a malpractice. So unless the patient is refusing treatment after discussing the key facts discussed herein, and the risk/benefits discussed herein, this initial treatment with the combination treatment should become the new standard of care.

Violation of that new standard of care would be a malpractice (unless the patient is refusing it after all the key facts discussed herein are presented to them).
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A) Summary for A) to E): In the following section we will critique the current diagnostic criterions for depression (that excludes many unrecognized [extended] depressive symptoms) and we will describe how to

recognize more depressed patients with a new test that includes extended depressive symptom list not found in the DSM criterion set. [That would also help psychiatrists and PCP's (the primary care doctors) to recognize depression more effectively]. We would follow that with B) describing a targeted conditioning effect with the added medication (atypical antipsychotics). [In Application Serial Number 11/034,447 we later named that targeted conditioning effect as pseudo-placebo effect, but the phenomenon as discovered by us was described in our provisional application and in our amended utility]. Under C) we will rely on these discoveries and of what was already known about relapse prevention in prior art (using the same information that we have already presented to the PTO in our prior reply). We would further that with D) on describing the clinical neuroplasticity phenomena and again of how the combination treatment would work based on what was already said under A) and B). We would further that even more with partial support described under E). All this is enabling even for the class of medications in our method and gives theoretical basis and rational of why our method can and should be used for the claimed purposes. So theory was provided to enable our application even for the broader sense (for the class of medications).
Please note that the mental health providers I shared this with had no problem understanding these principles:

One survey has revealed that about one third of respondents reported experiencing symptoms related to depression, however, only eighteen percent of the symptomatic group had ever been diagnosed. (Wallenstein G.V. et al., 2004.) It is also known that primary care doctors often miss the diagnosis of depression.
The provisional application, the amended utility and as further refined Application Serial Number 11/034,447 is addressing the solution of how we can improve on the recognition and testing for depression: It critics DSM and the current testing methods and draws attention to extended depressive symptoms that are not addressed in the DSM criterion set. Interestingly the combination therapy namely the atypical antipsychotics/dopamine system stabilizers are specifically targeting most of these extended symptoms that were left out in the DSM criterion set for diagnosing depression. So not only we can help more depression being recognized, but we can also support with this discovery the use of the combination treatment in the treatment of depression:

There is a misconception in DSM-IV, namely, that individuals only need to present with a subset of items from a longer list of criteria sets for the diagnosis (See e.g. DSM IV-TR p xxxii and 356, 375-376), therefore flawing the sensitivity of the diagnosis.
According to the DSM-IV, the diagnosis of MDD requires the presence of a major depressive episode (a building block to diagnose MDD and other mood disorders, such as bipolar disorder). This in turn consists of at least five of the nine symptoms present during the same two-week period, of which depressed mood or loss of interest or pleasure needs to be present as one of the symptoms.
Depression consists of a cluster of symptoms. This is reflected in the clinically used acronym provided by the DSM, "SIGECAPS," in which S = (is for) **decreased** (or increased) **sleep**, I = decreased interest, G = guilt, E = decreased energy, C = decreased concentration, A = decreased appetite, P = psychomotor retardation and S = **suicidal ideation**. (For an overview of the depressive symptoms and the mnemonic "SIGECAPS" see Carlat, D.J. 1998).

The misconception of the DSM with respect to depression is that instead of being a Diagnostic and Statistical Manual, it would be more appropriate to call it a Differential Diagnostic Manual. This is because, instead of a diagnosis, DSM provides sets of criteria to distinguish depression from other disorders, like anxiety, somatophorm disorder, or obsession, in which the sets of critera artificially create a specific disorder. For the purpose of differentiating depression from other mental illnesses, DSM is an excellent resource. However, the DSM criteria sets completely fail when it comes to recognizing and monitoring depressive symptoms during or after treatment to determine if the treatment is effective, if there is a remission or if there is a relapse of symptoms. Thus, the DSM falls short of what it is supposed to do, namely to screen, monitor and test the symptoms for depression. This failure is the result of not listing the appropriate amount of depression symptoms in the criterion part.

Nomenclatures like DSM are artificially created definitions. These definitions help psychiatrists to distinguish between anxiety disorders, depressive disorders, and thought disorders, such as psychosis. However, looking at the currently used depressive symptoms, such as a decrease in appetite or sleeplessness, one needs to ask how often do they occur and whether it really matters for purposes of making a diagnosis if these symptoms are not present. According to the DSM, one needs only five symptoms to make a diagnosis of depression. However, the frequently seen symptom in depression of anxiety is not required for diagnosis. This is because the DSM has artificially created another category for those anxiety disorders, referred to as a "comorbid disorder". In fact, it should be noted that anxiety is frequently more often present in depression than many other "depressive symptoms," but it is not included in diagnosing and treating depression. The same is true for other symptoms frequently present in depression that currently is not included in diagnosing depression, such as rumination, in which another category is created, referred to as the "OCD spectrum of disorders." Thus, depression is a mixture of many other symptoms that currently is not included in making the diagnosis, as well as being disregarded in treating the illness.

Therefore, our invention provides tools for an improved screening, monitoring and testing, and indirectly an improved treatment of depression, such as MDD, which includes the following extended symptoms:

Anxiety, including somatic symptoms. {A} {S}

Rumination (OCD symptom) (and focusing on negatives) – overlaps with rumination for guilt. (R}

Anger outbursts/impulsivity/hostility/violence, and resentments. {AHIV}

Cognitive distortion/global thinking. {CD}

Social **withdrawal**, which is different from a decrease of interest. {W}

Helplessness/hopelessness. This category is known but not included in the DSM-IV-TR. {H/H}

The atypical antipsychotics/dopamine system stabilizers may be useful for the treatment of all of the above extended depressive symptoms, either directly or indirectly, (as we have disclosed that in our amended utility).

Acute and chronic stressors, and the patient's ability to cope with them and to "problem solve" is another extended symptom that should be tested.

(In the search of new antidepressants, it has been recognized that stress and cortisol levels may play a role in depression, but this category has not been included in diagnosis or testing. {S}

Other symptoms and observed signs {O/O}: such as apathy, lack of feelings, affective unresponsiveness, also can be included in the testing. Also important are unchanging facial expressions; lack of verbal inflictions, i.e., monotone speech, poverty of speech or content of speech; decreased spontaneous movement, i.e., decreased gestures; poor eye contact; increased latency to respond; and thought blocking. Other signs of depression are difficulty reading, sustaining a conversation and collecting one's thoughts, as well as *difficulty falling asleep, or waking up at the middle of the night, which may also be related to rumination, i.e., automatic thoughts*. Other notable symptoms are lack of harmony and conflicting feelings.

Perception of unjust and resentment, with frequent, intrusive thoughts relating to this, also may be a symptom of depression. {U, R} This may be due, in part, because of a decrease in ego boundary accompanied with the increased exposure and vividly described and shown violent news, as well as unjusts broadcasted in the media. On the other hand, indifference {I,} and numbness, as seen in post traumatic stress disorder (PTSD), also may be present in depressed patients. Depressed patients may also tend to take things in life personally and to personalize insults, i.e. be overly sensitive. {S,}

A tendency for quick and impulsive decision making, i.e., shopping, overeating, or forming an opinion, also can be characteristic of depression, which overlaps with the cognitive distortion of "jumping to conclusions."

In summary, in addition to a depressed mood and "SIGECAPS" (sleep, interest, guilt, energy, concentration, appetite, psychomotor retardation, suicide), the extended list of depressive symptoms of our other invention includes a number of other symptoms that were ignored by DSM. No wonder that the primary care doctors miss diagnosing depression if many of the extended depressive symptoms are not looked for. No wonder that the rational was missed in prior art that the added atypical antipsychotics having effect on these (missed) extended depressive symptoms can affect recovery and prevent relapse by starting a cascade effect in the recovery.

B) In this section we will describe a targeted conditioning effect and a phenomena we discovered (that we later named as the "pseudo-placebo" – conditioning effect), and in this section we will describe how the atypical antipsychotics/dopamine system stabilizers can start a cascade effect for the overall improvement of the depression.
For the interest of the health care providers we shall also describe in this section how the atypical antipsychotics and dopamine system stabilizer are targeting multiple (extended) depressive symptoms, and with that in 2002 was supporting the use of these medications for the treatment of depression:

Certain (extended) depressive symptoms – Anxiety, Rumination (OCD symptom - focusing on negatives,) Anger outbursts/impulsivity/hostility/violence, Cognitive distortion/global thinking, Social withdrawal, Helplessness/hopelessness, as well as decreased sleep, and suicidal ideation – can specifically be targeted by medications (like the combination treatment). That would have additional positive cascade effect for global improvement in the patient's depression.
In this section we shall discuss the phenomenon and our discovery of how these medication effects on depressive symptoms causes a conditioning effect that is different from placebo. It is not a placebo, as a medication is specifically targeting a symptom, but it causes further psychological, expectation changes, a conditioning effect, therefore we used the term "pseudo-placebo" effect. This conditioning effect is furthering the global improvement of the patients.

Only one medication is used off label based on it's mechanism of eliciting a conditioned reflex, or as used herein a "pseudo-placebo" effect. Propranolol (Inderal), a beta blocker, titrated up to a higher dose, not only

reduces heart rate, but is used for impulse control, i.e., for aggression and violence. It works, by keeping the heart rate low even when people get angry and start acting out. This suggests, or gives a "false" feedback to the patient, that they are not in a flight or fight response situation, but rather everything is calm and "OK" because the patient's heart still is beating at a slow rate. The same principle applies when this medication is given for "stage-fright"/anxiety. This is not a placebo effect, as the medication has a specific pharmacological effect of slowing the heart rate down, and it is specifically selected for that action. However, it achieves it's desired action indirectly, relying on psychological principles like expectation and a conditioning effect. (It is noteworthy that propranolol has the potential side effect of mental depression, which may limit it's usefulness as an adjunct medication for depression).
Pindolol, a non-selective beta blocker, has been studied and used as an adjunct to some antidepressants in order to enhance the antidepressant effect giving a different explanation for its usefulness in those publications. This is noteworthy because if beta blockers act on anger/impulsivity/anxiety-fear i.e., within the extended depressive symptoms list, then any improved antidepressant effect could support the theory that it was the result of the "pseudo-placebo"/conditional reflex/expectation changing effect, even if it was pharmaceutically targeted.
Thus, when one targets depressive symptoms with various medications, besides having a direct effect on mood, the medications also may elicit a conditioned reflex, which is a reinforcement that change is possible, therefore improving hopelessness/helplessness and the patients' overall good feelings, the mood itself. Similarly to the action of propranolol, this is not a placebo, but rather a pseudo-placebo effect, which elicits a conditioned reflex and further change in the patient. Thus we present this novel phenomenon, which can be a key factor to better separate medication effects from placebo effects in drug development trials.

This new phenomenon is also important because it takes the focus away from explaining the reason of depression resulting in changes of neurotransmitters like 5-HT (serotonin) or nor-epinephrine (NE), and stresses the importance of targeting the extended list of depressive symptoms
It is known that changes in one neurotransmitter likely affects other neurotransmitters, and that our "simplified neurotransmitter theories" are more complex than once believed, e.g. many if not most neurons release more than one neurotransmitters (Trudeau, L-E. 2004). With the development of selective serotonin reuptake inhibitors (SSRIs), the role of serotonin in depression has been recognized. However, it is possible that it is really the NE that is the primary neurotransmitter implicated in depression, i.e. effecting mood per se, with serotonin being implicated more in the OCD component of depression, such as rumination and the pessimistic focus on the negatives, and having only a consequential secondary effect on the mood itself. Serotonin also has a role in learning and memory in the hippocampus. Appreciation of the pseudo-placebo effect can have further implications in clinical practice, patient education, marketing and new drug development. One example of this would be to shift our focus to medications that affect multiple neurotransmitters. Although current psychological tests do not show if one antidepressant is better than the other our new test with the extended depressive symptoms is likely to be more sensitive and should be used in particular to show the benefit of the combination treatment.
A high placebo response plays a role in the treatment of depression. The mean placebo response rate for major depressive disorder is about 30-40% with some studies reporting rates of 70% (Schatzberg A.F, et al., 2000). Some studies support that trend, showing that patients with more severe depression respond well to antidepressants whereas those mildly ill respond equally well to antidepressants and placebo (Khan, A., et al., 2002). Our understanding of the "pseudo-placebo - conditioning" effect is also important to better understand the high placebo response.
Since there are new antidepressants coming out with different mechanism of action (and so far without promise to show that their effect would be superior to the existing antidepressants), there is a risk that proper vigorous treatment could be withhold from some patients to just to "try out" these new medications.

Therefore raising awareness about the pseudo-placebo conditioning effect as well as about our new depression test with the extended depressive symptoms, can be important.

So let's see some other examples for this "pseudo-placebo" effect:

There are stories of the "miracle" effect of using stimulants as antidepressants in some medically ill/elderly patients (Kamholz, B.A., et al. 1996). (See also the reference for stimulant use in the medically ill/elderly: Satel, S.L. et al. 1988). A similar explanation – that was never put into this context before - may be involved here: that is by improving a patient's energy, i.e. correcting a depressive symptom, one sees a quicker response than with other antidepressants. With global improvement, the patient's expectation changes as well, and feelings of hopelessness become less pronounced or goes away entirely. This is another example for the "pseudo-placebo" conditioning effect.

Modafinil (Provigil), originally introduced as a wake-promoting agent for excessive daytime sleepiness associated with narcolepsy, may reduce tiredness/fatigue and sleepiness in depressed patients. This is another example that by targeting individual depressive symptoms one by one, a more rapid or more pronounced antidepressant effect can be achieved. This is also an example for the "pseudo-placebo" conditioning effect.

√ Addressing and relieving the anxiety which is present as a comorbid disorder in 56.8% of patients with known non-bipolar, major depressive disorder, can result in a drastic change in a patients' expectation of success. It is known that atypical antipsychotics/dopamine system stabilizers may be useful for relieving anxiety. Because a positive change has occurred, e.g., relief from anxiety and an improvement in their overall feelings, they would have more hope. Therefore, by pharmacologically addressing one symptom, improvement in other related symptoms, and in the depression generally, can be expected. This explains the subjective feeling of "immediate/ rapid" improvement from the psychological point of view, and why one should pay attention to the other depressive symptoms that are omitted from the DSM criterion sets. Thus, the "pseudo-placebo" conditioning effect - by having a pharmacological target and causing improvement in any of the depressive symptoms - would result in ameliorating another depressive symptom the helplessness and hopelessness. This in turn can have a cascade effect for the overall improvement of the depression.

√ Sleep disturbances, such as insomnia, is one of the symptoms often present in depression. Addressing this problem early on would similarly result in improved compliance and in a faster improvement

in the overall depressive symptoms. Temporarily adding a sleeping pill, such as zolpidem (Ambien), until the depressive symptoms, as well as the insomnia, lifts, can therefore have a more beneficial effect than the improvement of sleep per se. It is important to note that neuroleptics, in particular atypical neuroleptics, can improve sleep (Salin-Pascual, R.J. et al. 1999.) This again points to the benefit of combining these medications with antidepressants. Another reason can lead us to the same conclusion concerning the combination treatment because the antipsychotic-antidepressant combination has been used for treatment resistant obsessive-compulsive disorder (OCD). If one considers that rumination, one of the extended depressive symptoms, can be reduced with the use of these medications, then the sleep disturbance caused by rumination when going to sleep would also be eliminated.

Addressing cognitive distortions, anger attacks that 30-40% of depressed patients display, impulsivity, rumination, or social withdrawal are further examples of the pseudo-placebo conditioning effect, and the atypical antipsychotic antidepressant combination can be used to these symptoms as we have elaborated on this in our provisional patent application in 2002.

√ Depressed patients, because of their strong cognitive distortions, may not only misperceive information coming from the environment, such as miscommunications in their relationships that lead to social isolation, but also can misperceive stimuli coming from their own body. It is known that depressed patients have increased somatic symptoms (Stahl, S.M. 2002), with the majority of the depressed patients presenting only with physical symptoms to primary care providers. This demonstrates a support for the invention that depression also presents with a perceptual disturbance symptom, in which, just as for delusions, treatment with neuroleptics in combination with antidepressants can be useful. Therefore neuroleptics may be used to target this symptom and improve depression through the "pseudo-placebo" effect.

It is not polypharmacy that we advocate but a more vigorous treatment of depression, which improves patient satisfaction; provides a more rapid result in lifting depressive feelings and hopelessness, as well as anger and resentments that accompany depression, all of which would contribute to reducing the risk of suicide. More than one medication can be responsibly prescribed. As in all treatments, the final decision is always up to the patient and the treating clinician. Offering patients more than one option that includes the combination use of psychotropic medications can have many advantages. In this way, we are involving them in the decision-making, along with presenting the risks/benefits, side effects of the medications, and available alternatives.

Thus, the present invention places more weight on the use of medication combination, preferably by adding an atypical neuroleptic or a "dopamine system stabilizer."

In psychiatry, one is not afraid to prescribe more than one medication to patients, and the treatment of depression should not be an exception.

C) In this section - in relying of what we already said in A) and B) - we will discuss the relapse prevention rational of the combination treatment of antidepressant – atypical antipsychotics/dopamine system stabilizers:

Within the risk/benefit analysis, we should further educate the patients about relapse prevention. That should include the information that was known in prior art (and that we already disclosed to the PTO in a prior reply).
(1) compared to patients whose **antidepressants** were discontinued, those with **continued** treatment showed much **slower relapse risk,** so it is important to keep taking the medication(s). (Viguera, A.C. et al Discontinuing Antidepressant Treatment in Major Depression, Harvard Rev Psychiatry 1998; 5:293-306.)
(2)We should show to our patients that what facts would speak for that the combination treatment would prevent relapse:
We showed that there are many other depressive symptoms that the DSM ignores, and does not includes in its criterion list for depression. Yet these symptoms should be recognized as part of depressive symptom list. Targeting the relieve of these symptoms (with atypical antipsychotics or antidepressant-atypical antipsychotic combination) would result in the overall improvement of the patient.
It is also known that patients with **relative high level of depressive symptoms relapsed more often** than those who had little or no residual symptoms, (Cognitive therapy and pharmacotherapy for depression. Sustained improvement over one year. Simons A.D. et al, Arch Gen Psychiatry 1986; 43: 43-48)
Because the combination treatment is directly and indirectly affects many other (extended) depressive symptoms, it can be reasonably expected that they would result in less residual symptoms. This with our knowledge that little or no residual symptom is protective of relapse, would imply that the combination treatment would be effective in relapse prevention. So it is expected that the patients with the combination treatment would be protected from the relapse of depression, compared to the antidepressant monotherapy group.
Therefore, our synthesis, and our teaching on the unrecognized non-DSM symptoms, and that the antipyschotics are effective in relieving these "extended" depressive symptoms provides further enablement, to use this method and to give patients a better chance for full recovery and for a lower risk of relapse. Other publication have aslo shown that **fully recovered patients were at lower risk of relapse** (Thase M.E. et al Relapse after cognitive behavior therapy of depression: Potential implications for longer courses of treatment. Am J Psychiatry 1992; 149:1046-1052).

D) In this section we shall provide our novel education about the neuroplasticity of depression, and how that would further enablement of our claims and explain of why and how the combination method – as for the class of medications – would work. This also explains of how the combination treatment would enable our claims.
(We will also discuss how to minimize or remove the stigma against depression as mental illness, that in turn would result in more patients accepting treatment).
Nonadherence to prescribed medication accounts for as many as 20% of the cases considered to be treatment-resistant, and approximately 24% of patients do not inform their physicians that they have stopped taking antidepressants. (Demyttenaere, K. et al. 2001). Other publication reports that in primary care, more than one third of patients fail to refill their initial antidepressant prescription, and nearly half discontinue it within three months (Pincus, H.A., et al. 2001,).

While hopelessness as we described previously is one factor for the patients non-compliance, another major cause is the bias, the stigma against mental illness.
Many patients are against biological treatment and are either not receiving treatment or seek out natural and herbal remedies that were not tested by the FDA. Getting treatment for these patients means admitting of having the depression and thus the mental illness that they do not want to do.
Sharing with them information we are about to describe can be a successful strategy not only to educate them about depression but to remove or minimize the stigma it carries, and to make them our treatment acceptable:

[[This section in [[ ]] is optional and it was not in our provisional application:
There are various definitions of mental illness:
According to DSM if you have certain symptoms and meet the diagnostic criterion you qualify for depression and the mental illness. This however may not be the best definition, and would carry the stigma of the mental illness.
Another definition is that any condition causing an impairment in normal cognitive emotional or behavior functioning that is not part of normal development or culture would qualify someone for mental illness. That definition can be criticized as well and does not relieve people with depression from the stigma of mental illness.

All the above definitions are inadequate and misleading, as all of these focus on a condition affecting the mind as requirement for mental disorder. How about the patients who are not taking their blood pressure or diabetic medications and have a decreased insight? For strange reason while they have impaired judgment risking their own wellbeing and lives – thus an impairment in their "cognitive, and behavior functioning", they avoid the stigma of mental illness. In the public's eye the focus for these patients remains on their medical problems.

How about the following definition of insanity: - It is insane if we keep doing the same thing (that does not work or does not work so well) and we are expecting a different result? Well that would qualify almost all of us for having a mental disorder. Let us just point to ourselves to psychiatrists unwilling to change our viewpoints about the treatment of depression (just look at the algorithms), yet we are expecting a different, a better result and wonder that why so many of our patients are not getting better!
Now, I like that definition, as self-critique would get our patients' attention – and to that they would not display any self-defense or resistance.

There is another issue that is not talked about or shared with the patients: There is a continuum and a difference in quality among mental illnesses. The general public really consider for the definition of going insane if you hallucinate, have delusions and do not know what is real and what is not. Fluctuation in emotion is very humane. Gradual change goes unnoticed, as we get no feedback of getting different. It feels "it is just me". So in some ways there is a risk that during depression our mind can be also playing tricks us. Cognitive distortions (like the all or nothing thinking, jumping to conclusions) – that by the way is also seen in "normal" people – is more dominant in the depressed. But even in normal people our mind can also play tricks on us – just remember the black and white silhouette cut out pictures that you can view as either as two glasses or two faces facing each other.

So the better question is not about proving or disproving mental illness, but what are we going to do about it to get better and to get our depressed patients better.]]

In addition stories that depression can occur in anyone in certain situation, and showing of what happens in our brain in relation to these changes (a phenomena called neuroplasticity) can further take away the stigma against mental illness and thus make the biological treatment more acceptable. Moreover as we have seen in the case of [[pseudo-placebo]] targeted conditioning effect even the medications have some of their actions through psychological conditioning effect. When we are looking the global picture, and the role of neuronal plasticity in depression, the psychological and biological explanations indeed do blend together.

In an experiment unemployed actors were recruited for a depression study. They were paid volunteers, and were asked to act and think as-if depressed, to walk slowly with a bent posture, and think that they are no good, etc. In two weeks they have shown depression with the same changes in serotonin receptors in their platelet, as that was characteristic for depression in research studies. The actors reported that they had difficulty snapping out of the depression after the experiment was over.
This shows that depression would occur to anybody practicing being depressed, even in an "as-if" role-play situation. No one suggested before to use these examples to remove the stigma and self-blame about depression.

The Stanford Prison experiment done in the 1970's is better known. It was not designed to be a study about depression and it was never explained before as a study having implication for depression. Yet it is relevant.

It shows the importance of how detrimental a 'negative practice' can be, even in "as-if" (or role play) situations. In a Stanford experiment they recruited normal healthy volunteers who agreed to take part of a "prison simulation experiment" for up to two weeks. They randomly assigned them to be either "prisoners" or "guards". Unlike the guards, who had some minimal warm-up to the as-if event, 'the prisoners were covertly inducted, without their conscious cooperation. For the sake of "realism", they were arrested in the early morning, on false burglary charges, by actual members of the city police who were cooperating with the experimenters. The prisoners were then subjected to police interrogation and taken blindfolded to the simulated prison.' (Haney, C., et al. 1973, also referenced in Yardley, K.M. (1982 b),). The "prisoners" were further subjected to humiliating and frustrating experiences (and their queries to the police if this had to do anything with the experiment were ignored). After a week the experiment needed to be prematurely terminated, "due to the ensuing emotional disturbances amongst the participants, particularly amongst the prisoners". (Yardley, K.M. (1982 b),). The "prisoners" were feeling powerless, loss of control to the point of oppression, frustration, 'emasculation', anonymity, and arbitrary rule. The later in this case is really resulted in "learned helplessness" that we know as an important causative factor in the development of depression. While this experiment from the early 1970's looks cruel, and we can all hope that this kind of "experiments" can no longer be done today, they show the harmful effect of artificially being deprived of positive thoughts and emotions. This negative practice of focusing on the negatives, and to be forced to focus on the negatives, even in an "as-if" experiment, would result in an unwanted emotional disturbance. This is exactly the opposite of what we therapists and health care professionals want to achieve, and an example that "neuroplasticity" (the adaptation of brain to changes) works both ways. In a commentary on the above 'experiment' one author notes that the outcome would have been different if the participants would have been brought out of the as-if situation every few hours or so to remind them of the as-if framing. (Yardley, K.M. (1982 b),). That means of shifting the balance between the negatives and positives. This is what depression therapy is all about when we give the patients the tools of doing this.

Interestingly in some of the new reality shows there was no "break" in the "as-if" experiments and depression or symptoms of depression emerged in some of the participants:
[[We have added here some additional and optional examples to what we described in our provisional application, but that [or the omission of that] does not change the essence of the message that was covered.]]

In a PBS film ("1940's House"), where "volunteers" – a family, lived "as if living in 1940's war time London" in historical cloths, with old fashioned appliances, with simulated air raids, and mandated restrictions on their food supply ("as if there weren't enough"), the adult volunteer ("the mother") who stayed in this "experiment" reported depressed feelings. When she could volunteer outside of this role-play in contemporary peace time nursing home, she reported her depression being lifted. This too shows a similarity to the above two "as-if" experiments, opposite of what we therapists want to achieve, and is another example that "neuroplasticity" works both ways.
Depressive symptoms also occurred in another "as if reality show – with 24 hrs a day role-play, that was lasting for months". In that PBS' documentary the "Frontier House" (that was taking place under the re-enacted times and harsh condition of the American Frontiers") in one family, the mother expressed feeling depressed, and the father showed somatic concerns [frequently find in depression] – in this case about his weight loss. Interestingly, this was the family that "broke the agreed upon rules" of the role play, and made contact with the contemporary American society. Consequently they felt better in the later part of the "show" (i.e. their "as-if" experiment). It is also notable that from that point on the theme of the show also changed the participants having celebrations with feasts and plenty of food for the fall season. (That change in the theme

was possibly because of the involvement of child protective services behind the camera, since the reality show cannot starve the children of these families who were also participants and complained of the very real food shortage they had to endure of that re-enacted historical age, during the first part of the reality show).

So all of these points out that depression can occur to anyone.
Unfortunately that conclusion is not communicated to the depressed patients, who feel isolated, worried and is searching for the "why me" question.
False or misleading messages about the genetic susceptibility of depression would further contribute to self-blame, resisting the acceptance of having depression as a disease because of the stigma attached to it. We will correct the misleading messages about the genetic susceptibility of depression later, but let's examine first of what is happening in the brain regardless of how one gets depressed. Let's talk about the clinical neuroplasticity of depression.

Historically others concluded that because the therapeutic action of antidepressants requires weeks, - even though the antidepressant medications block the reuptake or metabolism of norepinephrine (NE) and serotonin (5-HT) much more rapidly - therefore the treatment of depression involves adaptation or plasticity of neural systems. (Duman, R.S. et al, 1999,).
In the depression research one of the primary interests is on the volume loss of the brain area called hippocampus, with possible neuron loss during depression. It had been questioned if stress and elevated glucocorticoid levels may cause that hippocampal neuron loss associated with subtypes of chronic depression. (Lee, A.L. et al, 2002; Duman, R.S. et al. 1999,). There is evidence that stress will cause a regression of dendritic process in hippocampal neurons – that is part of neurons connecting with other neurons – that is producing loss of neuronal volume. This however, has been shown to be reversible with the cessation of stress. (Lee, A.L. et al, 2002,).
The synaptic plasticity model of depression also overlaps with the theory on the failure of neurogenesis (that is lack of brain cell growth) linked to depression. (Vogel, G. 2000, Malberg J.E. 2004). Neuroimaging techniques show smaller hippocampi (brain area) in depressed patients, and antidepressant drugs and electroconvulsive therapy (in animals) show significantly more newly divided cells in the hippocampus. This is an addition to the recent discovery that had shown that the brain keeps producing new neurons into adulthood. (Vogel, G. 2000, Duman, R.S., et al 2000,).

So what we need to repeat is that the insult from stress and the brain changes in depression as these reports reveal are reversible with the cessation of stress and with the treatment of depression. (However, it is best to avoid that stress and depression as the recovery may not be 100%, the patient may be prone for subsequent relapse, or have a risk for residual symptoms. In other words 'neuronal connections did form while "practicing" to be depressed'. So it is easier to go back to the same place the second time if the paths have been already made before.) Yet, the point that needs to be emphasized is, that the recovery of depression is followed by brain changes. So the damage is not all permanent.

Let us first explain neuronal plasticity, the capacity of the brain to respond to changes. This phenomenon had been extensively studied in some other conditions where the cortical representations of somatic perceptions can be mapped. (Spitzer, M. 1999,) (As the brain has no sense of pain, neurosurgeons could operate on patients while they were conscious [in local anesthesia or "woken up" after their sculls were opened] for example to remove a tumor, but to preserve brain areas that are essential to speech, vision or movement. During such operations it was discovered that part of the cortex that is responsible for processing touch sensations and is representing the different areas of the body, has a map-like structure, called "homunculus" in the cortex. Not only touching, but all senses are represented in topographical cortical maps. [See also:

Spitzer, M. 1999,]).
The most intriguing is, that these cortical maps or cortical representations are not fixed, but have the ability to change if the input is changing (i.e. to show neuroplasticity). In a congenital malformation called syndactyly, the fingers are attached to each other (like in a fetal webbing). After the fingers are surgically separated, the borders between their cortical representations emerge in one week. (Mogliner et al. as referenced in Spitzer, M. 1999,). The opposite was also shown in animal experiments sawing the fingers together. Changes in cortical representation do follow this procedure.
In a different experiment (seen at PBS), a human volunteer was blindfolded for about two weeks, and it was found - through a non- or minimally invasive procedure, - that other brain areas started to "took over" the now unused visual cortex, and the cortical representations of the fingertips (touching) had increased.
It is interesting to compare that while it takes weeks for the antidepressants to start working, it also took week(s) to see neuroplasticity changes in the above experiments.

[[Similar cortical changes to the above animal experiments had been find in humans. It had been shown, that experienced violinists had a larger cortical representation of their fingers in their left hand compared to non-musicians as measured by magnetoencephalographic recordings. (Schlang et al referenced in Eisenberg L. TEN 2000, 2(4) 47-52).
Another example of the brain's ability to respond to environmental changes was found with magnetic source imaging. Blind Braille readers who read with three fingers had substantial enlargement of their topographical hand representation in the postcentral gyrus compared to one finger Braille readers and sighted non-Braille reading subjects (Sterr et al. referenced in Eisenberg L. TEN 2000, 2(4) 47-52).]]

Let's bring all what we learned above to the context of depression. Let's show a novel approach so that depressed patients can benefit from these stories.
So it is not only during depression or in recovery from depression that we see the brain adapt to changes. Practice or lack of practice also affects cortical representations.
In the following story, let's pay special attention to the "restraining mitt", the "practice makes a master" and to the "turning of dominos" parts that we can use as metaphors, easily pictured (and reminding) analogies in order to explain ways for recovery options in depression.

Traditionally it was believed, that if stroke victims did not regain the function of their arm within a few months, then it was little hope for recovery, we know it now that this is no longer true. Supported by clinical data and not just animal experiments, we know that persons with stroke "learn" of not to try using their paralyzed arms or legs, and as times goes on this becomes an increasingly powerful conditioned response. However, by placing a restraint (a large stuffed mitt) on the patient's functioning arm, he/she is forced to overcome the tendency of not using his/her weaker arm. With physical therapy they are coached 6 hours a day to practice and improve the movements of their weak extremity. They are given tasks like turning dominos over (and cheered for their success). With practice and repetition comes a dramatic change within a few weeks. This phenomenon had been explained as a result of "an increased recruitment of neurons surrounding the area of the primary damage caused by a stroke". The neurons that haven't been killed by the stroke, but are in the vicinity of the damage are sending out connections with other neurons. (Restak, R.M., 2001 and corresponding PBS video). This is the neuronal plasticity that we have also seen in other examples above.
In principles we see a similar phenomenon when children's good eye is covered to force the weaker eye to "learn to see". With practice we are relying on neuronal plasticity in a therapeutic way.
Now, if this true on other areas, why wouldn't it be true for depression, or for the treatment of depression?

The stories about the "as-if" experiments that we have shared above supports that most likely the same is true for depression.
Whether the actors playing all day long of being depressed, or whether someone is put in an adverse situation

(like the Stanford prison experiment or the adverse situation of reenacted war or harsh living conditions) that all results in reversible changes in the brain.

Depressed people tend to focus on the negatives, and tend to ignore seeing the positives. Cognitive therapy teaches us to do similar repetitions, that is, to catch ourselves to have (negative) automatic thoughts, and make necessary corrections by doing an analysis of the facts on both the negative and the positive side. This is the practice that is similar to the "practice makes a master" or "repetitions of the movements – turning the dominos" seen in stroke victims above. **We just do not have a good visible restraining "mitt" that would force us doing this practice. However medications** (and cognitive therapy) **do help exactly in that direction of restraining the negativistic thinking**: We have mentioned above, that the problem in depression is **rumination, the repetition and overt focus on the negatives**, with cognitive distortion. Actually SSRIs used for treating depression are also working to reduce OCD symptoms, "the rumination". (See also article about depression and rumination: Lyness J.M. et al., (1997). We have suggested that **atypical neuroleptics** may also be helpful in many ways (**including for rumination, as an adjunct to SSRIs**), and are expected to help decreasing cognitive distortions, that are so characteristic of and are contributing to the depression.
Please also note that the stroke victims have gotten 6 hours a day physical therapy. Compare this with the 45 minutes a week talking therapy session for the depressed if the insurance is paying for this at all. Most patients do not have access to well trained cognitive therapists (and the insurance does not pay their astronomical fees). So developing good self-help resources that bring innovations and new understanding about depression is also crucial.

The above stories supports the importance of practice to overcome depression. In this context the therapy of depression is very similar to the therapy of the stroke victims mentioned above. This "domino analogy" (or "practice makes a master") and "using the invisible restraining mitt" analogy can also be used clinically to motivate and educate patients about depression, and depression treatment.

The above stories can also give an insight to the course of depression, and to the 'natural' tendency to relapse. It also shows of **why is that so easy to relapse, if one stops taking the medication(s), or stops the 'positive "domino" practice'**. It was shown, that practicing cognitive therapy can be protective of the depressive relapse, and this is supportive of this view. It was also shown that the combination of antidepressant and cognitive therapy is superior to either treatment alone. [see Thase].
One of the reasons for why the neuroplasticity model of depression is still lagging behind is that our technology did not allow us to "**map**" the cortical representations and changes that occur with the depression. Our brain imaging techniques are improving (George, M.S. 1994, Ketter, T.A., et al. 1994, George, M.S., et al. 1994, Rubin, E., et al. 1994,), but there is another way to assess and "map" changes in the brain.
The cortical representation of one's "inner world" may be also reflected **by one's vocabulary**.
Assessing patients depression (or feelings) with a psychological test (a word list of synonyms expressing different degree of depression), can serve as a "mapping" tool. With an analogy it is like the vocabulary in the RAM or the hardware of speech recognition software. The words used (thoughts ruminated) more often are stored up front (RAM), but other words are still recognized that are stored in the hardware. So mapping of the neuroplasticity changes occurring during or in the recovery of depression is also possible with a psychological tool relying on the vocabulary of the patient.
In helping someone to come out of depression (and one's inner world of focusing on the negatives), it had been shown that physical exercise has a value, and have an antidepressant effect. (Russo-Neustadt, A., et al 1999, Blumenthal, J.A., et al 1999,). We also know, that in chronic pain, that frequently also overlaps with depression, physical activity has a beneficial effect. Moreover, physical exercise was also shown to be of

value in connection with learning and neuronal plasticity. These similarities are intriguing.
(If indeed exercise is having a neuroprotective effect that can be shown by imaging techniques (Colcombe SJ, et al 2003) than this would bring up the question that whether the **decreased volume changes** seen in the depressed is the consequence (in part) of the **psychomotor retardation "decreased exercise"**? Is it possible that **just like with the serotonin (neurotransmitter) change seen in the "as if experiments"** these **volumetric changes in the brain could not necessarily be a causative, but an accompanying factor** that could occur in anyone exposed to adverse environmental changes? – Or would these findings – i.e. from the depressive symptoms of psychomotor retardation isolation, (like decrease in exercise) just be contributory to the hippocampal changes seen in depression? It is also possible that the hippocampal volumetric and/or morphologic changes seen in depression is rather than being an effect from the change of mood per se, actually may be a result coming from the process of learning and/or memory, since learning is involved in the process of mental depression (learned helplessness model); and/or memory / cognitive deficits that are in the (extended) list of depression. All this new way of seeing the reasons for hippocampal changes in depression would fit in well with the findings that the hippocampus is involved in learning and memory, in which 5-HT and other neurotransmitters (NE, or NMDA receptor mediated responses) play a role. This recognition may also guide pre-clinical research for new antidepressants. (Focus may shift to the analysis of hippocampus and pre-frontal cortex in pre-clinical studies from the currently used animal models of depression). (Harvey, J.A. 2003, Meneses A. 2003, Coull, J.T. et al 1999, Rosenzweig, E.S. et al 2003).

It had been questioned before that if for the depressed patients everything would go exactly their way for a few solid weeks, without disappointments, rejections or criticism while everybody would love them, would their depression go away? (O'Connor, R. 2001 p23). Well, it depends. These circumstances could definitely make everybody's life easier, but recovery to a large extent depends on "the domino metaphor" or practice mentioned above. However, the "optimal circumstances" raised in the above question are so important that we should be teaching how to pay attention to our real needs, and how to get a harmony, a 'full life' not just recovery from depression.
In fact the closing remarks in a book where there is a lot of discussion about neuronal plasticity emphasizes that we all should "watch our mental diet". (Spitzer, M. 1999,). This means that we should watch the input we receive (e.g. through violent movies, discouraging news from within the society).

There are arguments for the genetic transmission of susceptibility for depression. However, a genetic transmission model cannot explain the increase in the rate of depression in the past decades. If depression is inherited, how come more of our children and even more of our grandchildren get depressed, and how come our parents and grandparents were relatively protected? Unfortunately this analysis is kept from the public, so depressed patients feel more hopeless and blame themselves and their genetic setups.
There is also data on stress and environmental events precipitating depression. Putting less emphasis on genetics and more on environmental variables (i.e. that there are things we can change) in patient education would also reduce the hopelessness, (the lack of control). In contrast to the "neurotransmitter deficit" explanation, this would less likely to generate the sense "that there is nothing that I can do about my genetic makeup, therefore about my depression". Therefore teaching the clinical neuroplasticity model of depression (above) [**the need for the invisible restraining mitt=meds**, (and/or cognitive therapy, catching cognitive distortions/ruminated thoughts), and the need for practicing (positive/corrected thinking=cognitive therapy], can be more helpful and increase the patients cooperation and therefore compliance.

This is in contrast to the neurotransmitter deficit/imbalance explanation as the sole (or main) reason for depression – e.g. see Zoloft's TV advertisement and patient education material). The neurotransmitter deficit (imbalance) would occur in (basically) everybody in reaction to a strong (negative) environmental effect (as

seen in the above "as-if experiments"). Therefore teaching the clinical neuroplasticity model of depression would also take away the "blaming, and self-blaming". Consequently it would take away the desperate efforts in some, to fight the 'acceptance' of a mental illness (depression) with its consequent refusal for medication. With this we could overcome one of the reasons why depressed patients do not seek treatment, why they discontinue their medications early, and why they are looking desperately for natural and herbal remedies instead of accepted and tested effective treatments. It would also take off the edge for the debate for "medication" – no-medication dilemma i.e. the struggle for fighting the disease without medication, the denial of mental illness, and the roots for its stigma.

What the most intriguing is, that the **environment does affect the expression of specific genes**, at least as it had been find in rodent pups. Maternal touch, licking, (or touch with a paintbrush) **affected gene expression** and lead to receptor changes compared to the deprived control group. (See E. Rossi).

In summary for this section in looking the global picture, that is the role of neuronal plasticity in depression, the psychological and biological explanations indeed do blend together.

This description - in contrast to the neurotransmitter deficit/imbalance explanation as the sole (or main) reason for depression - can increase patient compliance with medication, decrease the bias or prejudice in the public against mental illness, decrease the patients' resistance and inappropriate use of less effective treatment or no medication treatment because of the existing misperception (and hostility against biological psychiatry). Therefore, this method of description can decrease the percentage of treatment resistant depression.
For the purpose of enabling our claims, the bolded parts above should be focused on. That is the "invisible mitt" is the analogy of the combination treatment resisting the rumination, one of the extended depressive symptoms; (as it was shown before that it is useful for treating treatment resistant obsessive compulsive disorder [OCD]). If we stop the "positive practice" or in the analogy not use the combination treatment to effectively handle rumination (OCD symptom), the said natural tendency of relapse can manifest. So in indirect way, our novel neuroplasticity explanation of depression is also supporting enablement.

E) Last but not least in this section we will describe a partial support for enablement, that starting the treatment (in the most effective way) right away would decrease the patients' hopelessness and helplessness (therefore target additional [extended] depressive symptoms. The more symptoms we address right away the better the chances of full recovery (and for preventing relapse).
[With this we will also describe a strategy to get more patients accept and adhere to treatment]:

Depressed patients in general have the basic believe that why bother, nothing works, they have helplessness and hopelessness, that may explain in part of why more than one third of patients fail to refill their initial (antidepressant) prescription, and nearly half discontinue it within three months in primary care. (Pincus, H.A., et al. 2001,).
Therefore it is essential to give patients an immediate reinforcement and a new personal experience that change is possible.

One way to do that is to start the combination treatment right away and give the treatment the patients need. An immediate improvement in any of the patient's symptoms is a direct reinforcement that change is possible, which changes the patient's expectation.
Let's admit that the "standard" assessment of a depressed patient was so far to ask a lot of questions

concerning painful or negative aspects of the patient's life, almost a dwelling in the patient's problem, and give no immediate relief for the patient's symptoms. In fact typically at the end of the first visit when we gave the prescription, we used to tell the patients that it may take weeks for the antidepressant to work. As a result negative expectations were reinforced and because of their hopelessness many have discontinued taking their medications.

Nonadherence to prescribed medication accounts for as many as 20% of the cases considered to be treatment-resistant, and approximately 24% of patients do not inform their physicians that they have stopped taking antidepressants. (Demyttenaere, K. et al. 2001). Other publication reports that in primary care, more than one third of patients fail to refill their initial antidepressant prescription, and nearly half discontinue it within three months (Pincus, H.A., et al. 2001,).

Many psychiatrists were willing to wait twelve weeks after two consecutive monotherapy trial before concluding treatment-resistance and considering an add on medication. Since the rate of residual symptoms or missed or inadequately treated depression is high no wonder that the patients loose hope and develop an attitude that nothing works. It is high time changing this old practice!

So this number E) argument is different from the reasoning given under the "mock trial" but also supports a vigorous treatment, to give patients an immediate reinforcement and a new personal experience that change is possible for which the combination medication (and to give the treatment the patients need) is one such solution. We can further that by also providing the patients with new information about depression as we presented this herein that gives them hope and helps them accepting treatment.

So in summary again for A) to E): In section A) we critiqued the current diagnostic criterions for depression (that excludes many unrecognized [extended] depressive symptoms) and we described how to recognize more depressed patients with a new test that includes extended depressive symptom list not found in the DSM criterion set. [That would also help psychiatrists and PCP's (the primary care doctors) to recognize depression more effectively]. We followed that with B) describing a targeted conditioning effect with the added medication (atypical antipsychotics). [In Application Serial Number 11/034,447 we later named that targeted conditioning effect as pseudo-placebo effect, but the phenomenon as discovered by us was described in our provisional application and in our amended utility]. Under C) we relied on these discoveries and of what was already known about relapse prevention in prior art (using the same information that we have already presented to the PTO in our prior reply). We furthered that with D) on describing the clinical neuroplasticity phenomena and again of how the combination treatment would work based on what was already said under A) and B). We furthered that even more with partial support described under E) of why starting the treatment of depression in the most effective way is so important from another point of view. All these are enabling even for the class of medications in our method(s) and gave theoretical basis and rational of why our method can and should be used for the claimed purposes. So **theory was provided to enable our application even for the broader sense (for the class of medications).**

So it seems that we have satisfied the requirement asked by the examiners, and we have supplied the required theory and enablement in a broader sense (for the class of medications – antidepressants and atypical antipsychotics. As a result, it is respectfully submitted that our Claims – as amended - **are in proper form for issuance** of a Notice of Allowance and such action is respectfully requested at an early date.

We are also **asking the examiners for claim drafting assistance so that the broader – and enabled – class of medications could also be included in the claims similarly like it was originally in the earlier versions of our claims** (claims 1 and 2). We would propose to insert this either in lieu of the earlier cancelled claims 44-47 or if that is technically not allowed then as new claims 148, 149, 150, 151, and we would pay for the new claims if needed. Please also read the revisited issue on the "as soon as possible" in the next paragraph after the proposed [to be added] claims.

We are providing here two versions for the proposed claims as an example, to facilitate the examiners in the claim drafting assistance (It is possible that all of the provided proposed claims should have been underlined):

> On 12-6-10 the IAC [ref# 1/179367602] has helped with the fee calculation, new claims are $110, claims $26, and cancelled claims and cancelled multiple dependent claims can be counted as already paid fees. [If calculation would be wrong by any chance I would get a letter to send the fee.]

Claims – to be added – as preferred (see New claims 148-151):

148. (New): [formerly 1. (Original)/amended herein]: A method for treatment of a patient suffering from major depressive disorder, the method comprising administering to said patient an effective amount of an antidepressant in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of an atypical antipsychotic drug, and a dopamine system stabilizer, and wherein said major depressive disorder categorized as non-treatment resistant and non-psychotic.

149. (New): [formerly 2. (Original))/amended herein]: A method for treatment of a patient suffering from unipolar depression, the method comprising administering to said patient an effective amount of an antidepressant in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of an atypical antipsychotic drug, and a dopamine system stabilizer, and wherein said unipolar depression categorized as non-treatment resistant and non-psychotic.

150. (New): [formerly 41. (Currently amended)]: The method of Claims 148 or 149, wherein treatment is given for resisting suicide.

151. (New): [formerly 42. (Currently amended)]: The method of Claim 149, wherein treatment is effected for at least one of the group consisting of inhibiting the development of tolerance toward the antidepressant, remedying the development of tolerance toward the antidepressant, avoiding a paradoxical effect of antidepressant sensitizing patients to depression, avoiding worsening of depression from the antidepressant, and treating worsening of depression from the antidepressant.

Or **if the above proposed claim 44 (formerly 1) and if the above proposed claim 45 (formerly 2) would not be allowed** then as alternative we propose the following claim and claim language to be added (taken from the response to the 1st OA): (this is less preferred to the proposed claims in page 33)

[or as 148] [formerly 1. (Original)/amended herein]: A method for treatment of a patient suffering from major depressive disorder, the method comprising administering to said patient at a time selected from the group consisting of, as an initial treatment, as soon as possible and upon presentation of said patient to a physician or other health care provider an effective amount of an antidepressant in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of an atypical antipsychotic drug, and a dopamine system stabilizer, and wherein said major depressive disorder categorized as non-treatment resistant and non-psychotic.

[or as 149] *[formerly 2. (Original))/amended herein]:* A method for treatment of a patient suffering from unipolar depression, the method comprising administering to said patient at a time selected from the group consisting of, as an initial treatment, as soon as possible and upon presentation of said patient to a physician or other health care provider an effective amount of an antidepressant in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of an atypical antipsychotic drug, and a dopamine system stabilizer, and wherein said unipolar depression categorized as non-treatment resistant and non-psychotic.

[or as 150] *[formerly 41. (Currently amended)]:* The method of Claims 148 ~~1~~ or 149 ~~2~~, wherein

treatment is given for ~~preventing~~ resisting suicide.

[or as 151] *[formerly 42. (Currently amended)]:* The method of Claims ~~1 or~~ 2 149, wherein treatment is ~~given~~ effected for at least one of the group consisting of ~~preventing disease progression, modifying the course of depression, delaying/preventing relapse, preventing the recurrence of depression, protecting against~~ inhibiting the development of tolerance toward the antidepressant, ~~or~~ remedying the development of tolerance toward the antidepressant, ~~to provide providing a neuroprotective effect, to avoid~~ avoiding a paradoxical effect of antidepressant ~~to sensitize~~ sensitizing patients to depression, ~~to avoid~~ avoiding worsening of depression from the antidepressant, and ~~or treat~~ treating worsening of depression from the antidepressant, ~~to treat and treating residual symptoms of depression, or for preventing the development of delusional/psychotic depression~~.

At page 7 of the last OA pages 15-17 the PTO again revisits the issue of "as soon as possible":
"Note that "as soon as possible" is an extremely broad limitation that would include practically any method wherein treatment was not deliberately delayed".
Please note that at the reply to the 6th OA (March 11, 2010) page 21 [starting with paragraph b) to page 22 that had been already addressed. Let us reiterate here the most pertinent parts from our prior reply:
"The "as soon as possible" is still within the timeframe that has been specified at the end of the claim: "wherein said major depressive disorder categorized as non-treatment resistant and [non-psychotic]". (We have given a definition in our specification for what treatment resistant means and what time frame it involves.)
"As soon as possible", the "initial treatment", "and upon presentation of said patient to a physician or other health care provider" puts an emphasis on the beginning of that time frame that is otherwise limited and described as non-treatment resistant. Actually this is further limiting the preference with that emphasis, putting more stress to the start of the episode (rather then suggesting using the treatment on the last day, that technically still does not fall within the treatment resistant category). The skilled in the art should understand that nobody is talking about milliseconds difference in the "as soon as possible" description, but in the context of the specification the "as soon as possible" may refer to that after gaining the patient's agreement and cooperation and after discussing the risk/benefit alternative analysis... The "as soon as possible" may also refer to the availability of the medication or if the patient declines the medication and there is another chance to re-discuss with the patient the risk/benefit/alternatives, then the "as soon as possible" time period shifts to the next available opportunity. I really do not think that the description of what "as soon as possible" means in this context would create a conflict."

Line by line reply:

We would follow similar formatting as in the line by line reply to the prior office actions.
For better organization, we put our brief reply in tables. Indented to the left or left column is the copy of the 7th office action's pertinent part, indented to right or right column is reference or our brief reply to the 7th office action (incorporating/referring to the above replies).
Please also refer back to our comments made before the line by line reply (so that we can avoid unnecessary repetition).

Application/Control Number: 10/627, 358 Page 2 Art Unit: 1623 Continued Examination Under 37 CFR 1.114 A request for continued examination under 37 CFR 1 . 114, including the fee forth in 37 CFR 1 .17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1 . 114, and the fee forth in 37 CFR t . 17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1 . 114. Applicant's submission filed on March 15, 2010 has been entered Detailed Action This office action is a response to applicant's communication submitted March 15, 2010 wherein claims 1 , 2, 42, 48, 53, 54, 59, 100, 122, 123, 130, 134-140, 142, and 144 are amended and claim 9 and 65 are cancelled. This application claims benefit provisional application 60/319436, filed July 30, Claims 1 -8, 10-38, 41-43, 48-64, and 66-147 are pending in this application Claims 1 -8, 10-38, 41 -43, 48-64, and 66-147 as amended are examined on merits herein Applicant's amendment, submitted March 15, 2010, with respect to the rejection of instant claim 65 under 35 USC 1 12, first paragraph, for introducing new matter into the disclosure, has been fully considered and found to be persuasive to remove the rejection as claim 65 has been cancelled. Therefore the rejection is withdrawn Application/Control Number: 10/627, 358 Page 3 Art Unit: 1623 Applicant's arguments, submitted March 15, 2010, with respect to the rejection of instant claims 1-9, 11-12, 37, 38, 41 -43, 48-50, 53-71 , 96-103, 126, 131-145, and 147 under 35 USC 112, first paragraph, for lacking enablement for all of the claimed classes of compounds, have been fully considered and found to be persuasive to remove the rejection as all of the claimed classes of compounds are known in the art to be useful for treating patients suffering from depression and would have been available to one skilled in the art. Therefore the rejection is withdrawn Applicant's arguments, submitted March 15, 2010, with respect to the rejection of instant claims 1 , 2, 4, 6, 10-15, 18, 22, 26, 30, 36-38, 41 , 42, 48, 51-53, 56, 58-60, 109- 118, 124, 125, and 140-143 under 35 USC 103(a) for being obvious over Tollefson et al '921 , has been fully considered and found to be persuasive to remove the rejection as a review of the prior art indicates that the clinical trial described by Tollefson et al involved schizophrenic patients. Specifically, the non-patent reference Tollefson et al (Reference included with PTO-892) discloses further information concerning the same clinical trial and indicates that he subjects were schizophrenic Therefore the rejection is withdrawn Applicant's amendment, submitted March 15, 2010, with respect to the rejection of instant claims 1 - 3, 9, 11-15, 37, 38, 41 -43, 48, 49, 53-62, 69-74, 96-105, 129, 142, and 145 under 35 USC 103(a) as being obvious over Robertson et al. in view of Merck, has been fully considered and found to be persuasive to remove the rejection as the Application/Control Number: 10/627, 358 Page 4 Art Unit: 1623 claims have been amended to exclude methods using typical antipsychotics Therefore the rejection is withdrawn. Applicant's amendment, submitted March 15, 2010, with respect to the rejection of instant claims 106-107 under 35 USC 103(a) as being obvious over Robertson et al in view of Berman, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to exclude methods using typical antipsychotics. Therefore the rejection is withdrawn. Applicant's amendment necessitates the following new grounds of rejection	It was addressed above and in prior replies to OAs.

Claim Rejections - 35 USC $ 112 The following is a quotation of the second paragraph of 35 u.s.c. 112 The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention. Claim 69 is rejected under 35 u.s.c. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention This claim specifies that the antipsychotic drug is selected from the group consisting of perphenazine, trifluoroperazine, zotepine, fluphenthixol, amisulpride, and sulpride. These are typical antipsychotic drugs However, this claim depends from claims 55 and 57, which depend from claims 1 and 2, which require that the antipsychotic be an atypical antipsychotic or dopamine system stabilizer Therefore claim 69 contradicts the limitations of its parent claims, creating confusion as to what its true scope is and rendering the limitations of this claim indefinite.	Claim 69 was cancelled.

Application/Control Number: 10/627, 358 Page 5 Art Unit: 1623 The following rejections of record in the previous office action are maintained Claim Reiections - 35 USC $ 112 The following is a quotation of the first paragraph of 35 u.s.c. 112 The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention. Claims 140, 141 , 143, and 144 are rejected under 35 u.s.c. 112, first paragraph, as failing to comply with the written description requirement The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention Applicant's amendment submitted March 13, 2009 with respect to the aforementioned claims has been fully considered and but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for a method comprising discussing all of the specific considerations recited in the claims with a patient. Although the specification and the priority document 60/319436 do disclose these factors as considerations for physicians to take into account in the treatment of depression, they do not teach or disclose discussing them with a patient As the instant specification as filed contains no description of this method the specification as originally filed does not provide support for the subject matter of instant claims 140, 141 , and 143. See in re Smith, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972)	It was addressed above. We have shown that this is not a new matter and gave explanation for the reasons.

Application/Control Number: 10/627, 358 Page 6 Art Unit: 1623 **Claim Rejections - 35 USC $ 103** The following is a quotation of 35 u.s.c. 103(a) which forms the basis for all **obviousness rejections** set forth in this Office action: (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made. Claims 1 -6, 11 , 13, 37, 38, 41-43, 48, 49, 53, 54, 56, 58, 59, 119-121 , 123, 126-129, 142, 145, and 146 are rejected under 35 u.s.c. 103(a) as being unpatentable over Howard. (US patent publication 2002/0123490, of record in previous action)	It was addressed above and in prior replies to OAs.

Howard discloses a combination of a serotonin reuptake inhibitor and an atypical antipsychotic, as well as a method for using this combination to treat obsessive compulsive disorder, psychosis, and depression. (p. 1 , paragraph 0004) Depressive disorders treated include major depressive disorder, as well as atypical depression including anxiety. (p. 1 , paragraph 0008) Anxiety is reasonably considered to be as cognitive distortion as it involves disordered cognitions such as overestimation of risk Although treatment of refractory depression is a preferred embodiment, all depression including depression not found to be refractory, is included within the range of disorders to be treated The amounts of each agent used are such that the combined effect has improved efficacy compared to either component individually. (p. 1 paragraph 0005) Atypical antipsychotics used in the invention include abaperidone, belaperidone, clozapine, iloperidone, olanzapine, perospirone, risperidone, sertindole, tiospirone, ziprasidone, zotepine, quetiapine, and blonanserin. (p. 7 paragraphs 0172-0198) The	It was addressed above and in prior replies to OAs.
Application/Control Number: 10/627,358 Page 7 Art Unit: 1623 two agents are to be administered in dosages of about 5-200 mg/day of the antipsychotic agent and about 2.5-500 mg/day of the serotonin reuptake inhibitor. (p. 8 paragraph 0233) The compounds can be administered by various dosage forms including oral administration. (p. 9 paragraphs 0235-0236) Howard does not specifically disclose a method wherein the therapeutic agents are administered as soon as possible. It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Howard as an initial therapy and/or to administer it as soon as possible One of ordinary skill in the art would have been motivated to practice the invention in this manner because Howard already discloses the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art **Note that "as soon as possible" is an extremely broad limitation that would include practically any method wherein treatment was not deliberately delayed.** Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art Thus the invention taken as a whole is prima facie obvious.	It was addressed above and in prior replies to OAs.
Application/Control Number: 10/627, 358 Page 8 Art Unit: 1623 Claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81 , 85, 89, 95-105, 109-122, 124, 126-130, and 142 are rejected under 35 u.s.c. 103(a) as being obvious over Chappell et al. (US patent application 10/001 827, Pub. Number 2002/0094986 A1 , of record in previous office action) Chappell et al. discloses a method of treating depression, anxiety, or psychosis in a mammal by administering a combination of an antidepressant, a D4 receptor antagonist, (an antipsychotic) and a pharmaceutically acceptable carrier. (p. 1 , left column, paragraph 0002) Note that anxiety is reasonably considered to be a cognitive distortion as it involves unreasonable patterns of thought, namely excessive or irrational worry and exaggeration of problems or threats Phobias and panic disorders are also considered to be cognitive distortions. General types of antidepressants which can be used are listed in paragraph 0021 and include norepinephrine reuptakenhibitors,	The D4 receptor issue was discussed in details in the applicant's replies to previous OAs.

serotonin reuptake inhibitors, and monoamine oxidase inhibitors, among others, as described in instant claims 11 -13. Selective serotonin reuptake inhibitors include fluoxetine, fluvoxamine, paroxetine, and sertaline. (p. 3, paragraph 0025) Norepinephrine reuptake inhibitors which may be used are listed in paragraph 0023 and include clomipramine among others, as in instant claims 14 and 15 Other useful antidepressants are listed in paragraph 0181 on p. 8. The compounds used in this invention may all be administered orally, as described by instant claim 38. (p. 22, paragraphs 0460-0462) Various dopamine D4 receptor antagonists can be used, as listed on pp. 15-21. In particular, p. 20, paragraph 0446 lists olanzapine as a useful D4 receptor antagonist D4 receptor antagonists can be administered in a preferred dose Application/Control Number: 10/627,358 Page 9 Art Unit: 1623 of about 5 to about 500 mg per day. (p. 22, paragraph 0459) Chappell et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider Chappell et al. does not disclose a method where in the antipsychotic is administered in a dose of 2.5-10 mg olanzapine. It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Chappell et al. as an initial therapy and/or to administer it as soon as possible One of ordinary skill in the art would have been motivated to practice the invention in this manner because Chappell et al. already discloses the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art It would also have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Chappell et al. using a dose of 5-10 mg of olanzapine per day One of ordinary skill in the art would have been motivated to use this range, and would have reasonably expected success in doing so, because the range disclosed by Chappell et al. significantly overlaps with the range of the claimed invention, which is considered to represent Applicant's low dose regimen When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See /n re Wertheim, 541 F 2d 257, 191 USPQ 90 (CCPA Application/Control Number: 10/627,358 Page 10 Art Unit: 1623 1976); /n re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP S 2144.05 [R-1l. Further, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art Thus the invention taken as a whole is prima facie obvious. Claims 106-108, 131-134, and 136-139 are rejected under 35 u.s.c. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001 827, Pub. Number 2002/0094986 A1 , of record in previous office action) in view of Berman et al (Reference of record in previous action) The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method in which the antidepressant is ketamine. Berman et al. discloses that ketamine, which acts on the NMDA receptor, exerts antidepressant effects in human patients. (p. 351 , second paragraph, right	It was addressed above and in prior replies to OAs.

column, P 352, left column, last paragraph, p. 353, right column, first paragraph)
It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as the antidepressant in the method of Chappell et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the antidepressants recited by Chappell et al. One of ordinary skill in the art would
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reasonably have expected success because Ketamine is already known to be useful as an antidepressant
Thus the invention taken as a whole is prima facie obvious.
Claims 5, 16, 17, 20, 21, 24, 25, 28, 29, 32-35, 64, 75, 76, 79, 80, 83, 84, 87, 88, 91 -94, 123, and 125 are rejected under 35 u.s.c. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001 827, Pub. Number 2002/0094986 A1 , of record in previous office action) as applied to claims 1 - 4, 6, 10-15, 18, 22, 26, 30, 36-38, 41 -43, 48, 49, 51-63, 66, 70-74, 77, 81 , 85, 89, 95-105, and 109-122, 124, and 126-30 above, and further in view of Schmidt et al. (Reference of record in previous action)
The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method using ziprasidone, risperidone, or quetiapine as the antipsychotic agent. Schmidt et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p- 198, table 1) In particular, ziprasidone, risperidone, olanzapine, and quetiapine are all shown to have affinity for the D4 receptor. It would have been obvious to one of ordinary skill in the art at the time of the invention to use ziprasidone, risperidone, or quetiapine as the dopamine D4 antagonist in the invention of Chappell et al One of ordinary skill in the art would have recognized that these compounds possess the same biological activity, namely D4 antagonism, required by the invention of Chappell et al., and can thus be used as therapeutic agents
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in this invention Applying a known therapeutic agent in this way to a known therapeutic method, is part or the ordinary and routine level of skill in the art
Thus the invention taken as a whole is prima facie obvious.
Claims 5, 16, 20, 24, 28, 64, 75, 79, 83, 87, and 125 are rejected under 35 u.s.c. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001 827, Pub. Number 2002/0094986 A1 , of record in previous office action) as applied to claims 19, 6, 10-15, 18, 22, 26, 30, 36-38, 41 -43, 48, 49, 51 -63, 66, 70-74, 77, 81 , 85, 89, 95-105, and 109-122, 124, and 126-30 above, and further in view of Roth et al. (Reference of record in previous action)
The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method using risperidone, trifluoroperazine, or zotepine as the antipsychotic agent Roth et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 366, table 1) in particular, risperidone, olanzapine, trifiuoroperazine and zotepine are all shown to have affinity for the D4 receptor It would have been obvious to one of ordinary skill in the art at the time of the invention to use risperidone, trifluoroperazine, or zotepine as the dopamine D4 antagonist in the invention of Chappell et al One of ordinary skill in the art would have recognized that these compounds possess the same biological activity, namely D4 antagonism, required by the invention of Chappell et al., and can thus be used as
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It was addressed above and in prior replies to OAs.

therapeutic agents in this invention. Applying a known therapeutic agent in this way to a known therapeutic method, is part or the ordinary and routine level of skill in the art Thus the invention taken as a whole is prima facie obvious. Claims 1 , 2, 4, 5, 6, 10-14, 16-18, 20-22, 24-26, 28-30, 32-38, 41-43, 48, 49, 51-64, 66, 70-77, 79-81 , 83-85, 87-89, 91-105, 109-122, 124-129, and 145-147 are rejected under 35 u.s.c. 103(a) as being unpatentable over Pivac et al. (Reference included with previous action) in view of Merck (Reference of record in previous action) Pivac et al. discloses that atypical antipsychotics such as risperidone or olanzapine, should be coadministered with selective serotonin reuptake inhibitors, because they produce a synergistic effect. (p. 236, left column, last paragraph, right column first paragraph) Pivac et al. does not disclose a therapeutic method using the specific SSRIs fluoxetine, paroxetine, sertaline, or fluvoxamine, or the atypical antipsychotics ziprasidone or quetiapine Pivac et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering a low dose of the antipsychotic Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine Merck et al. also discloses a listing of atypical antipsychotics, including Application/Control Number: 1 O/627,3S8 Page 14 Art Unit: 1623 clozapine, risperidone, olanzapine, quetiapine, sertindole, and ziprasidone. (p. 1570, table 193-4) It would have been obvious to one of ordinary skill in the art at the time of the invention to use the various SSRIs and atypical antipsychotics disclosed by Merck in the method of Pivac et al. One of ordinary skill in the art would have recognized that the specific compounds disclosed by Merck fall within the broad classes described by Pivac et al., and can thus be used in the disclosed method Substituting these known prior art compounds in a known prior art method is well within the ordinary and routine level of skill in the art It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Pivac et al. as an initial therapy and/or to administer it as soon as possible One of ordinary skill in the art would have been motivated to practice the invention in this manner because Pivac et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art Finally, it would have been obvious to one of ordinary skill in the art to administer the antipsychotic in a low dose One of ordinary skill in the art would have been motivated to administer the lowest effective dose of the drug because of the well known side effects of typical antipsychotic drugs. One of ordinary skill in the art would have Application/Control Number: 10/627,358 Page 15 Art Unit: 1623 reasonably been able to adjust the dosage of the compounds administered to	It was addressed above and in prior replies to OAs.

achieve the optimal result while minimizing toxicity from the drugs themselves Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art
Thus the invention taken as a whole is prima facie obvious.
Claims 1-4, 7, 8, 10-15, 19, 23, 27, 31 , 36-38, 41-43, 48, 49, 51-63, 67, 68, 70-74, 78, 82, 86, 90, 95-105, 109-122, 124-130, and 145-147 are rejected under 35 u.s.c. 103(a) as being unpatentable over Jordan et al. (PCT international publication WO02/060423, reference of record in previous action) in view of Merck. (Reference of record in previous action) Jordan et al. discloses a method of treating a patient suffering from a disorder of the central nervous system associated with the 5-HT1A receptor, comprising administering a compound having a given structure. (p. 15, lines 5-18)
According to the Chemical Abstracts Registry entry 129722-12-9, (reference of record in previous action) this structure is aripiprazole This compound is useful for treating various disorders of the central nervous system, for example major depression and melancholia, as well as various cognitive distortions including obsessive compulsive disorder, alcohol and drug addiction, and cognitive impairment. (p. 16, line 23 - p. 17, line 10) The preferred unit dosage form is 1 -20 mg of active agent. (p. 18, lines 5-10)
Jordan et al. does not disclose a method comprising administering aripiprazole in

combination with an antidepressant. Jordan et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering 2.5-15 mg of aripiprazole.
Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine.
It would have been obvious to one of ordinary skill in the art at the time of the invention to co-administer the antidepressants of Merck with the typical antipsychotics of Jordan et al. to a patient suffering from major depression either alone or complicated by any of the various cognitive distortions recited by Jordan et al One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder Combining two known prior art therapies is well within the ordinary and routine level of skill in the art.
It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Jordan et al. as an initial therapy and/or to administer it as soon as possible One of ordinary skill in the art would have been motivated to practice the invention in this manner because Jordan et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is

indicated One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.
It would also have been obvious to one of ordinary skill in the art at the time of

It was addressed above and in prior replies to OAs.

the invention to practice the method of Jordan et al. using a dose of 2.5-15 mg of aripiprazole per day One of ordinary skill in the art would have been motivated to use this rang, and would have reasonably expected success in doing so, because the range disclosed by Jordan et al. significantly overlaps with the range of the claimed invention, which is considered to represent Applicant's low dose regimen When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See In re Wertheim, 541 F 2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F 2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP S 2144.05 [R-11. Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art. Thus the invention taken as a whole is prima facie obvious. Claims 106-108, 131-133, and 135-139 are rejected under 35 u.s.c. 103(a) as being unpatentable over Jordan et al. (Reference of record in previous action) in view of Berman et al. (Reference of record in previous action) The disclosure of Jordan et al. is Application/Control Number: 10/627,358 Page 18 Art Unit: 1623 discussed above Jordan et al. does not disclose a method in which the antidepressant is ketamine. Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351 , second paragraph, right column, p. 352, left column, last paragraph, P 353, right column, first paragraph) It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as an antidepressant in combination with a typical antipsychotic recited in the method of Jordan et al One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al reveals that ketamine is useful for the same purposes as the therapies recited by Jordan et al., namely treating depression One of ordinary skill in the art would reasonably have expected success because ketamine is already known to be useful as an antidepressant. Thus the invention taken as a whole is prima facie obvious. Claims 3-5, 10-15, 20, 28, 37, and 50-52 are rejected under 35 u.s.c. 103(a) as being unpatentable over Theobald et al. (US patent publication 2003/0049308, first published as PCT international publication WO01/80837) Theobald et al. discloses a transdermal or transmucosal patch comprising nicotine and a further active substance, that is useful for treating nicotine dependency, for nicotine substitution, or for disaccustoming smokers. (p. 1 , paragraphs 0002, 0003, and 0009) The additional active agent can include antidepressants or neuroleptics Application/Control Number: 10/627, 358 Page 19 Art Unit: 1623 (antipsychotics), for example chlorpromazine, perphenazine, sulpride, clozapine, clomipramine, doxepin, risperidone, paroxetine, or fluvoxamine. (p. 2, paragraphs 0015-001 7) Theobald et al. does not explicitly exemplify a method comprising administering said patch comprising nicotine, an antidepressant, and an antipsychotic It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Theobald et al. using nicotine in combination with both an antidepressant and an antipsychotic One of ordinary skill in the art would have been motivated to practice the invention in this manner because each of the additional agents (the antidepressant and the antipsychotic) is revealed individually by Theobald et al. to be useful in combination with nicotine for the treatment of nicotine addiction	It was addressed above and in prior replies to OAs. Theobald simply has a laundry list of medications to be used for transdermal patch and does not enables our method does not give any guidance, explanation or rational of why it could be used for the purposes of our claims. **As we said before citing a patent book:** In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures." "A disclosure is non-enabling if it fails to place the subject matter of

Adding both of these agents at once to the disclosed invention is well within the ordinary and routine level of skill in the art and carries a reasonable expectation of success in achieving the desired therapeutic goal

Thus the invention taken as a whole is prima facie obvious.

Response to Arguments

Applicant's arguments submitted March 15, 2010, with respect to the above grounds of rejection have been fully considered and not found to be persuasive to remove the rejections. Arguments are addressed herein below.

Rejection for new matter:

Applicant argues that claims 140, 141, 143, and 144 do not introduce new matter because the specification and the provisional application both disclose discussing risk/benefit alternatives with the patient. However, the applicant has not cited specific passages from the specification or provisional application which disclose these methods Applicant also requests specifics of exactly which words the examiner objects to However, the problem with these claims is not certain specific words but rather the very nature of what is being claimed These claims are directed toward a method of interacting with a patient, and are really separate and distinct from the actual therapy being administered to the patient. The goal of the pharmacological therapy is to treat depression and reduce the risk of suicide The goal of the doctor-patient interactions in claims 140, 141 , 143, and 144 is to educate the patient as to the reasons for administering a particular therapy.

In the instant case, although the provisional application contains some arguments that are similar to the ones presented in these claims, the arguments in the provisional application appear to be directed toward convincing the audience of health care practitioners to adopt a particular standard of care. While it is of course part of good clinical practice to discuss the rational behind a therapy with the patient, the claims recite certain Specific arguments and rationales that the practitioner should make. In effect, these claims are directed toward a method of convincing a patient to comply with a therapy. Convincing those of skill in the art to adopt a particular standard of care is a separate undertaking from convincing a particular patient to comply with that standard of care. It is not clear that the same arguments will be convincing in both

cases, as the concerns of a patient are different than those of a practitioner and the level of knowledge and experience in the art is different as well Therefore arguments made in the patent specification to convince other skilled practitioners to adopt a standard of care are not seen to provide written description for a method of using those same considerations to educate a

the claims within the possession of the public, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).)

If the references are not each directed toward solving the same problem to which the invention is also directed, then the rejection should be withdrawn. (In re Rouffet, 149 F.3d 1350 [Fed. Cir. 1998].) (Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 223.)

It was addressed above and we showed why this is not a new matter.

patient about a therapy.	

Rejection for Enablement: Applicant's arguments regarding the enablement of the various classes of therapeutic agents recited in instant claims 1 -3 have been considered **The rejection of these claims for lacking enablement has been withdrawn** as it is concluded that all of the classes of antidepressant compounds recited in the claims are classes of compounds that one skilled in the art would have had access to and been able to use for the treatment of depression based upon these compounds' known pharmacological effects. Furthermore, regarding the standard of enablement applied to the cited prior art references, the instant claims were rejected for lacking enablement over their full scope For a claim to be enabled, it must be enabled for every embodiment encompassed by the claims For example, a claimed method utilizing antidepressants must be enabled for using any possible antidepressant whatsoever in order to be allowed In the case of a prior art reference, however, a reference is anticipatory if it enables at least one embodiment falling within the claimed method. For example, if the prior art discloses a method using antidepressants, but is only enabled for using serotonin reuptake Application/Control Number: 10/627,358 Page 22 Art Unit: 1623 inhibitors, it would only be prior art for a method of using serotonin reuptake inhibitors However, the fact that the prior art lacked enablement for other embodiments would not prevent its being used as prior art for what it was enabled for This can create the illusion of a double standard, in which a term is rejected as non-enabled over its full scope in a claim but then considered enabled for one specific embodiment in a prior art reference However, in both cases, the broad genus is considered non-enabled and the specific embodiment is considered enabled. **It is never alleged that previously known antidepressants, for example citalopram, paroxetine, fluoxetine, and so forth, are non-enabled** One skilled in the art would know based on the state of the art that they can be used clinically, whether in Applicant's method or in a prior art method, whether or not a particular reference specifically reiterates all that is known in the art about the compound Enablement is less clear, however, for broad functionally defined categories of active agent, for example a claim directed toward antidepressants in general In such a case, one skilled in the art would have to know all different classes of antidepressants and their limitations, side effects, therapeutic indications, drug interactions, and the like,in order to be able to use the full scope of all possible compounds in the invention Figuring out all of these uncertain factors would require an immense burden of unpredictable experimentation and the discovery and characterization of many new antidepressants In short, there is a lower standard of enablement for a mention of a specific active agent or combination of active agents (paroxetine) than **for a broad functionally defined class of agents, (antidepressants)** as it requires no undue or unpredictable experimentation Application/Control Number: 10/627,358 Page 23 Art Unit: 1623 for one skilled in the art to simply look up a specific compound in the primary literature or in other reference materials in order to confirm that it possesses therapeutic activity Of course the recitation of a seemingly absurd embodiment (e.g. treating depression with aspirin) would lack enablement	As the PTO said: "**The rejection of these claims for lacking enablement has been withdrawn**" It was addressed above and in prior replies to OAs.

unless the reference gives specific reasons to believe that the embodiment is enabled, either **by providing a plausible theoretical basis** or convincing experimental data for the embodiment Because all of the prior art references make mention of specific active agents which are already known to those skilled in the art, they are enabled as prior art at least for those specific agents.	It was addressed above and in prior replies to OAs. We did provide the theoretical basis for the broader class of medications, thus enabled broader claims.

Prior art rejections: In the case of the Theobald reference, the reference is considered to be enabled for the specific antidepressants and antipsychotics recited in the reference, regardless of whether the reference is enabled for the broad classes of antipsychotics and antidepressants generally. In considering the eight Wands factors mentioned in previous office actions, the teachings of the prior art, the level of skill in the art, and the predictability of the art are sufficient in the pharmaceutical art that one skilled in the art could look up these compounds and determine their therapeutic indications, drug interactions, optimal doses, and so forth The reference itself does not need to spell all of these things out in full detail. Application/Control Number: 10/627,358 Page 24 Art Unit: 1623 Regarding the Jordan reference, it is repeated that the bar for enabling a specific compound or structurally related set of compounds is lower than that needed to enable a broad functionally defined class of compounds Considering that a convincing line of reasoning has been established (by analogy with gepirone) that 5HT1A agonism could treat depression, it would not require an undue burden of unpredictable experimentation to determine whether the compounds of Jordan et al. had an antidepressant effect, for example using animal models such as the forced swim test or chronic mild stress model Enablement does not require that a compound have passed clinical trials so long as the amount of experimentation needed to practice the invention is merely routine verification of facts for which evidence already exists. Regarding the Chappell et al. reference, Applicant argues that the reference does not address the secondary factors recited in the claims such as protecting against the development of tolerance toward antidepressants, avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression, avoiding worsening of said depression from said antidepressant, treating worsening of said depression from said antidepressant and said antidepressant causing suicidal ideation, these limitations do not further limit the claim because they are not manifest in any actual concrete limitation of the method steps For example, a limitation on the patient population (e.g treatment resistant or non-treatment resistant patients), a specific dosage level, or a particular timing of administration, or co-administration with a particular second active agent, are all concrete limitations on the breadth of the claimed method. The instant Application/Control Number: 10/627,358 Page 25 Art Unit: 1623 claims, for example, clearly do not encompass administering antidepressants and antipsychotics to psychotic patients. Neither do they encompass antidepressant monotherapy. However, what is the concrete difference	It was addressed above and in prior replies to OAs.

between the actual method steps undertaken in a method where the practitioner intends to avoid the paradoxical effect of said antidepressant sensitizing said patients to said depression and a method where the practitioner does not intend said effect? If a limitation is not manifest in the actual positive actions taken while performing the method, it does not further limit the claims, as purely mental processes are not patentable	It was addressed above and in prior replies to OAs.

Factors involved in a determination of obviousness: While the cited prior art references have been addressed previously, the general rationale behind the finding of obviousness is presented here The factual inquiries set forth in Graham v. John Deere co., 383 u.s. 1 , 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 u.s.c. 103(a) are summarized as follows 1. Determining the scope and contents of the prior art. 2. Ascertaining the differences between the prior art and the claims at issue 3. Resolving the level of ordinary skill in the pertinent art. 4. Considering objective evidence present in the application indicating obviousness or nonobviousness. The scope and contents of the prior art - antipsychotic agents including atypical antipsychotics are known in the art as being usable for treating depression, typically in combination with an antidepressant, as described in the aforementioned references. The most common use of this combination is in treatment resistant, psychotic, or bipolar Application/Control Number: 10/627,358 Page 26 Art Unit: 1623 depression, but several patent references make mention of unipolar depression or major depressive disorder as a broad category which can be treated by antipsychotic therapy, for example the reference Howard US2002/01 23490 The differences between the prior art and the claims - none of the prior art references specifically recommend using antipsychotics as initial therapy **in a treatment- naive non-psychotic depressed patient** who has not previously failed to respond to antidepressant monotherapy Rather the prior art is silent as to where in the treatment regimen the antipsychotic should be introduced. The level of ordinary skill in the art - A typical practitioner is skilled in the pharmacological treatment of psychiatric disorders and is familiar with the available literature on psychiatric drugs such as antidepressants and antipsychotics Furthermore, although these drugs are approved for certain specific indications, one skilled in the art is capable of using them off-label if a suitable rationale exists for doing so, and can perform cost-benefit analysis to determine if the expected benefit from such therapy outweighs the risks in a particular patient The question as to which therapeutic approach to try first falls within such a cost-benefit analysis. Objective evidence indicating obviousness or non-obviousness in the application - The application contains a lengthy discussion of the treatment of depression and the inadequacies of current treatment guidelines, particularly as regards the incidence of suicide While the evidence indicates a clear need for an improved treatment of depression, the application does not in fact provide data showing that the	It was addressed above and in prior replies to OAs. Please note that our claims never restricted the use of our method to treatment native patients. Patients who had been on antidepressants and have another episode, or otherwise do not meet our exclusion criteria are included in our claims.

claimed treatment strategy would in fact constitute an improvement over the prior art While this Application/Control Number: 10/627,358 Page 27 Art Unit: 1623 might be the case, until proven by factual data, it is insufficient to provide evidence of secondary considerations in favor of patentability **Secondary Considerations:** Applicant has repeatedly made the argument that the failure of those skilled in the art to actually practice the invention indicates that the invention is not obvious Applicant's reasoning appears to be the following a) Those of ordinary skill in the art are concerned about the risk of suicide in depressed patients and will use the best available therapy to prevent suicide b) The claimed method is clearly superior to the current standard of care for treating depression c) Those of ordinary skill in the art do not in fact use the claimed invention in clinical practice therefore: d) The claimed invention is not available (i.e. non-obvious) to those of ordinary skill in the art, or else they are unaware that it is superior to the current standard of care ln technical terms, Applicant is alleging that the claimed invention satisfies a long-felt unsolved need or that it has an unexpected benefit over the prior art Both of these arguments can be used to overcome a finding of prima facie obviousness However, either of these findings requires evidence that the claimed invention actually Application/Control Number: 10/627, 358 Page 28 Art Unit: 1623 solves the long-felt need or produces the alleged unexpected results, in order to establish part b) of the above syllogism After all, if an invention is not superior to the prior art it is not surprising if it is not used in clinical practice. There is nothing surprising about the failure of those in the art to use a method that is not superior to the present standard of care. Applicant's disclosure gives arguments as to why an antipsychotic might augment treatment of depression However it provides no clinical data to establish whether or not this hypothesized effect is in fact real. Therefore Applicant has not demonstrated unexpected results or satisfaction of a long-felt need. Since Applicant appears to be a skilled practitioner in the art, it is possible that Applicant has actually treated as significant number of patients off-label using the claimed therapeutic method. lf this is the case, and the results obtained were clearly superior to those seen in the prior art for the current standard of care, (e.g. antidepressant monotherapy) then an affidavit or declaration under 37 CFR 1 . 132 summarizing the results obtained in Applicant's own practice and comparing them to what has been observed in the prior art, for example in clinical trials of antidepressant monotherapy, could suffice to establish unexpected results and the satisfaction of a long-felt need. Such results could take the form of an observation of reduced suicidality, faster onset of antidepressant effect, or improved response rate, for example.	It was addressed above and in prior replies to OAs. (This is the PTO's and not the applicant's summary)

Furthermore, a prima facie case of obviousness can be overcome if the prior art teaches away from modifying the prior art in the claimed manner. In the instant case, Application/Control Number: 10/627,358 Page 29 Art Unit: 1623 the prior art teaches an antidepressant effect for antipsychotic medications or combinations of these medications with antidepressants. However as mentioned previously the prior art does not specifically recommend using these agents as an initial therapy Therefore if it were established that he prior art specifically criticized or discouraged using antipsychotics as initial therapy, this could overcome the finding of obviousness It is suggested that if Applicant is aware of publications representative of the state of the prior art, for example clinical guidelines or review articles, that specifically disparage or criticize the use of antipsychotics as initial therapy for non-psychotic depression, that submitting these publications in an information disclosure statement could overcome the finding of obviousness if the references are sufficient to establish a widespread consensus in the art at the time of filing against using the claimed invention as initial therapy. It is also suggested that if such evidence is introduced, the claims may have to be amended so as to be commensurate in scope with the evidence For example, if the evidence concerns only the use of one particular class of antidepressant, such as serotonin reuptake inhibitors, it may serve to prove non-obviousness only for claims drawn specifically to that particular class of drugs. If Applicant considers either of these approaches to be feasible for overcoming the obviousness rejections, it is suggested that he contact the examiner to discuss the Application/Control Number: 10/627,358 Page 30 Art Unit: 1623 specific contents of such a declaration of information disclosure statement before filing any further amendment in this application. Conclusion No claims are allowed in this application. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. OLSON whose telephone number is (571)272-9051 The examiner can normally be reached on Monday-Friday, 8 30-5:00 If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627 The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system Status information for published applications may be obtained from either Private PAIR or Public PAIR Status information for unpublished applications is available through Private PAIR only For more information about the PAI R system , see http.#pair-direct. uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571 -272-1000 /Eric S Olson/	It was addressed above and in prior replies to OAs.

Before the examiners would be **addressing the amended claims below** <u>please also refer back to pages 33-35</u> with the additional claims to be included and request about claim drafting assistance.